The American Journal of Medicine

January 1948

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The American Journal of Medicine

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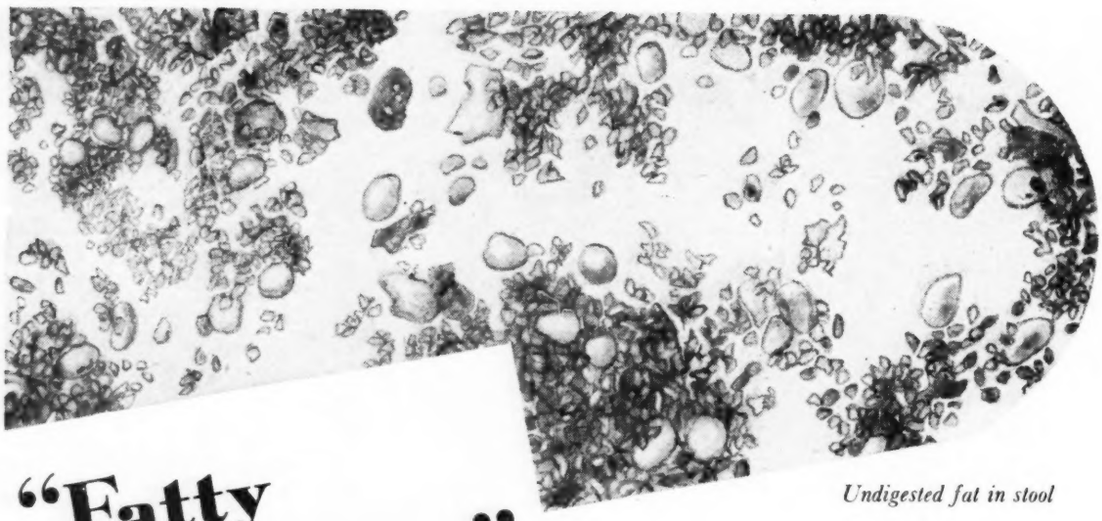

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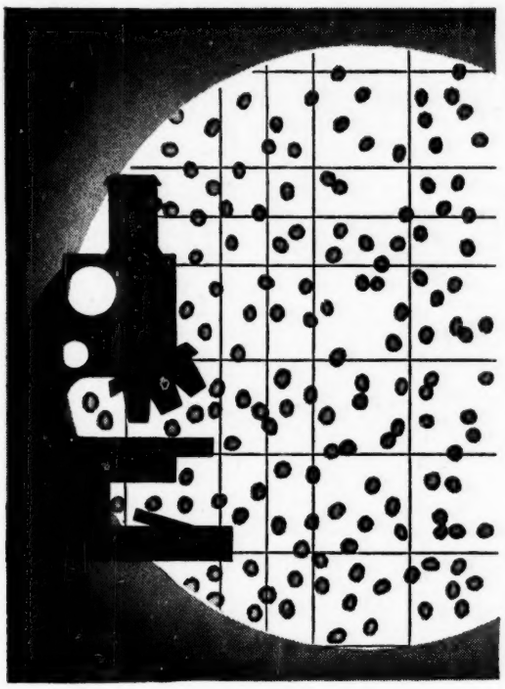

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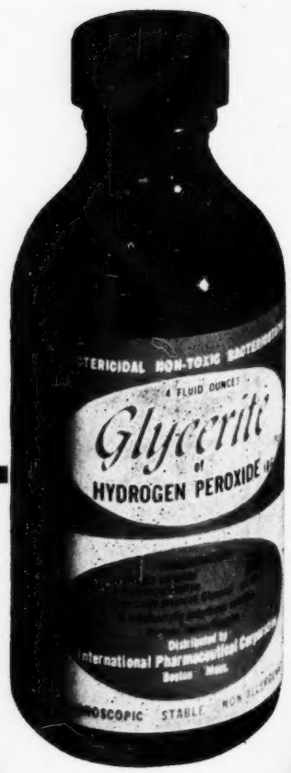

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J. Invest. Derm.	8:11, 1947.
Annals of Allergy	4:33, 1946.
Science	105:312, 1947.
J. Bacteriology	Vol. 53, June, 1947.

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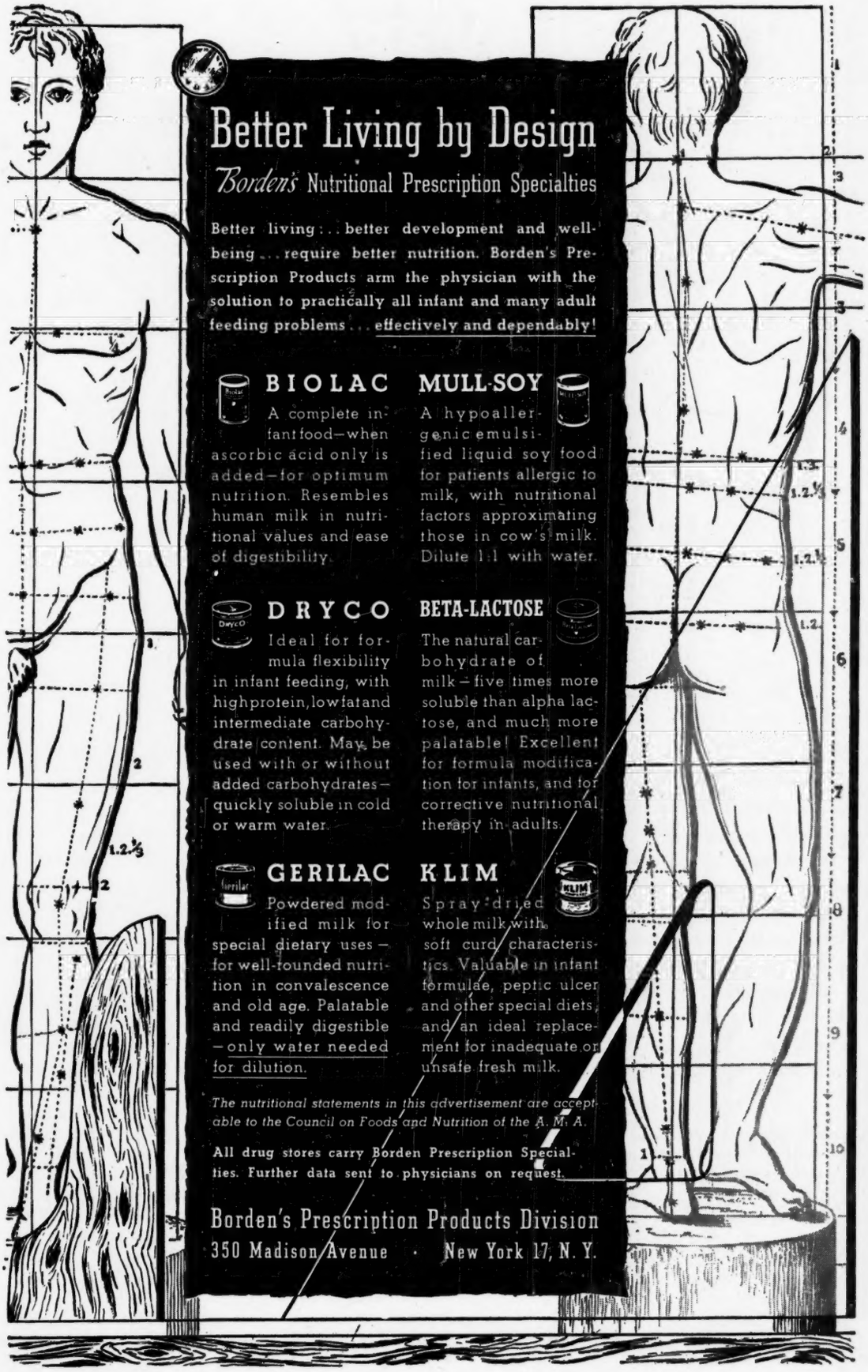

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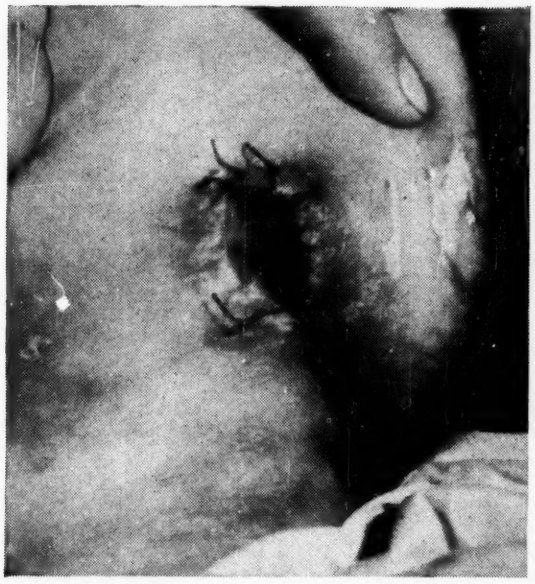

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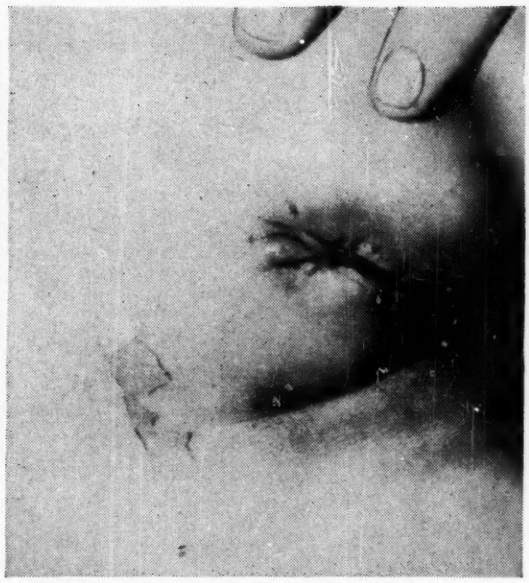

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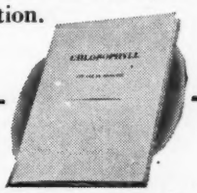

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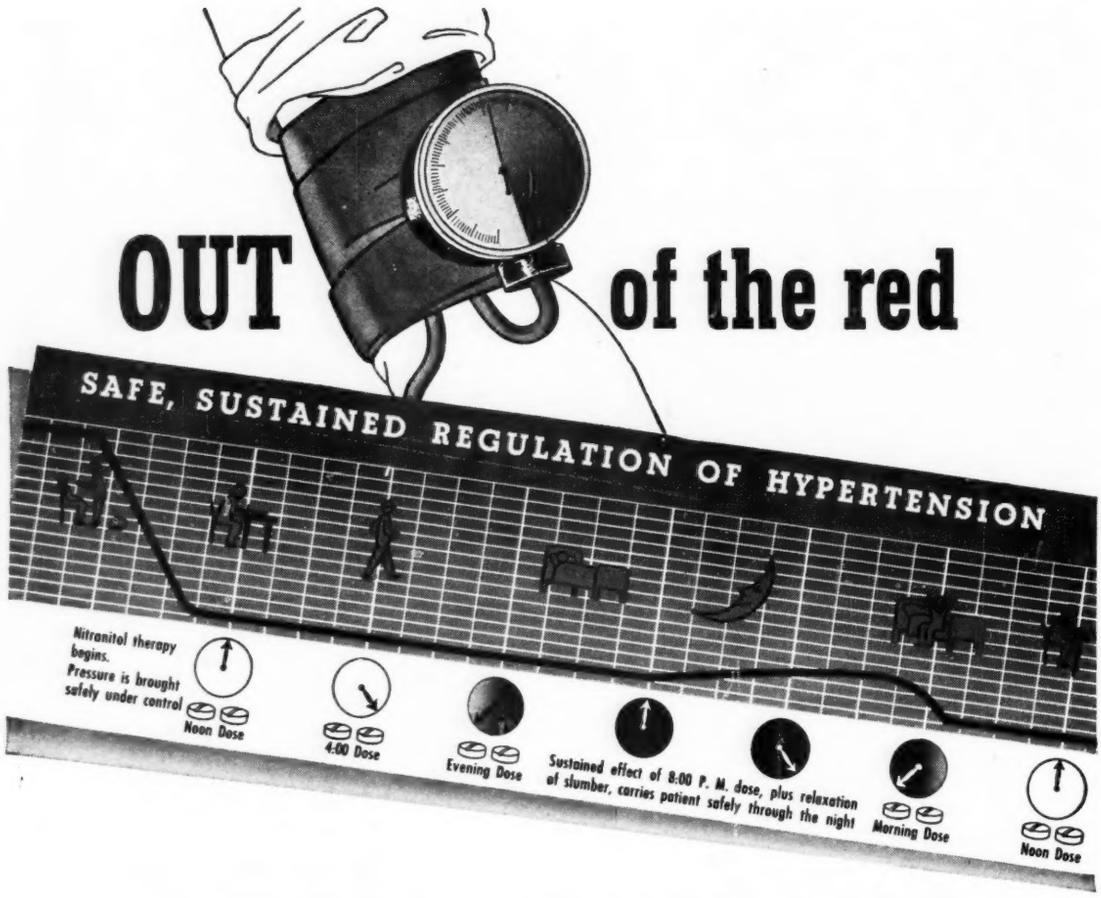

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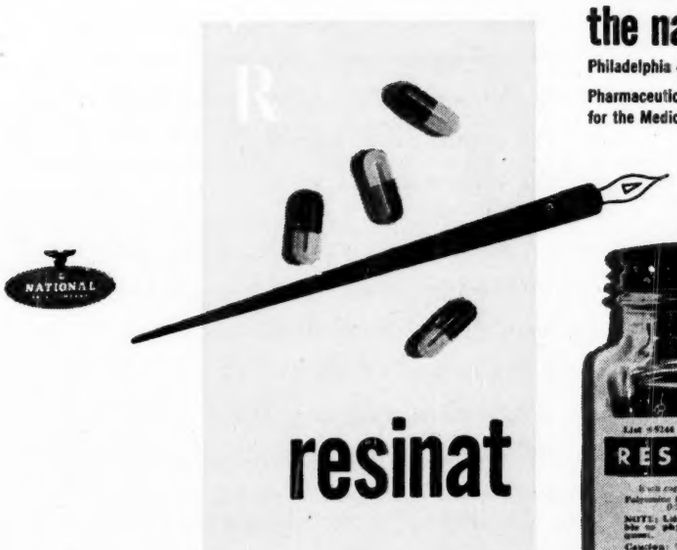

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Saunders, 1945, p. 559
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The American Journal of Medicine

VOL. IV JANUARY, 1948 No. 1

Editorial

BAL (British Anti-Lewisite)

THE history of specific antidotes to poisoning by metals is substantially an account of unfulfilled promises. The long succession of failures was interrupted, however, in the early days of World War II by a series of important discoveries made in rapid succession in the cooperative war programs of chemical, pharmacologic and clinical research focused on the problem of an antidote to the arsenical vesicant, Lewisite. The chief practical issue was the synthesis of the compound BAL which is not only highly effective in preventing tissue damage by arsenic and mercury but also in reversing moderate grades of tissue injury after the metals have been at work for some time.

The numerous lines of investigation leading to this discovery were recently reviewed by Peters, Stocken and Thompson of Great Britain, and by Waters and Stock of this country. Many important steps were necessary before the problem arrived at the point at which an effective antidote became available. One of the earliest observations bearing most directly on the subject was that of Voegtlin, Dyer and Leonard of the United States Public Health Service who, in 1923, advanced the view that the therapeutic arsenicals produce their effects by combining with the —SH groups of protoplasm. There were observations that various enzyme systems depended on the free —SH group for their activity, that these enzyme systems could be poisoned by arsenicals, that the combination in some types of thioarsenites could be reversed in alkaline solution, that monothiol and some dithiol compounds with arsenic were as toxic as the arsenical itself; observations leading to the belief that fairly stable but reversible ring compounds might be formed between the arsenical and the —SH groups of tissue proteins or the protein portion of the enzyme systems and that similar but less easily dissociable compounds of the arsenicals are formed by their interaction with simple dithiols which can compete successfully with the tissue dithiols for the toxic metal.

The compound 2,3-dimercaptopropanol, more popularly known as British anti-Lewisite or BAL, is not a harmless material. It is itself a poison. It is an irritant to the skin and mucous membranes and in large doses causes death with capillary paralysis and shock, sometimes preceded by convulsions. It causes lacrimation, blepharospasm, salivation, vomiting, muscular cramps, unrest, apprehension and weakness. Small doses produce arteriolar constriction with elevation of the blood pressure. It is noteworthy that unpleasant effects are produced by doses much below those which may cause serious damage, a fact which provides an element of safety against overdosage. BAL is rapidly eliminated in animals and man and doses may be repeated in man at intervals of three or four hours without significant cumulation. Studies in man show that some of the minor toxic effects may be produced by doses as small

as 3 to 5 mg. per Kg. although single doses as high as 8 mg. per Kg. have been given with safety by intramuscular injection. BAL may be used by most of the common routes of administration, subcutaneous, intramuscular and intravenous injection, dilute applications to the eye and by skin inunctions. It is best given by intramuscular injection in the form of a 10 per cent solution in peanut oil.

In human poisoning with arsenical compounds, the administration of BAL gives rise to a prompt and marked increase in the arsenic content of the blood which is associated with a marked increase in the arsenic excretion in the urine. There now exist convincing reports on the value of BAL as an antidote against dermatitis, encephalitis, agranulocytosis and the various febrile reactions due to the arsenicals. There is some doubt concerning its utility in arsenical jaundice. The best results are obtained when the antidote is given fairly promptly after the poison has been taken but it proves effective even after considerable injury has been produced by the arsenical.

The problem has been carried to the field of other metals and evidence has been obtained in the laboratory that such heavy metals as lead, antimony, vanadium, bismuth, cadmium, mercury and zinc inactivate —SH-containing enzymes and that these effects can be reversed by members of the BAL series.

Considerable advance has been made in the application of BAL as an antidote to bichloride of mercury poisoning. The results of experiments in rabbits and dogs by Gilman and his collaborators showed a high degree of protection against the systemic effects of mercury even when treatment was delayed for two or three hours, indicating that the dithiols may remove mercury from its combination with the cell proteins. BAL has been applied successfully by Longcope and his collaborators in the treatment of patients with bichloride of mercury poisoning. Again, while the best results are obtained when the antidote is administered soon, dramatic relief of symptoms and complete recoveries occurred in patients treated with BAL under conditions which rarely allowed for recovery with any previous forms of treatment. In a fairly large series of cases of poisoning at the Johns Hopkins Hospital in which the patients swallowed 1 Gm. of bichloride of mercury or more, and admission was delayed for periods up to four hours, all those treated with BAL recovered while the mortality rate in similar controls was about 30 per cent. BAL has also been shown to be effective against the toxic effects of the organic mercurial salyrgan in the mouse, the cat and the dog. This is of considerable importance in view of the extensive use of these diuretics and the possibility of accidental overdosage.

There seems to be very little doubt of the efficacy of BAL as an antidote to arsenic and mercury poisoning. Isolated observations have already been made on the effect of BAL in human poisoning by other metals, copper, zinc and gold. Several rather striking results have been reported on the use of BAL in poisoning produced by gold employed in the treatment of arthritis.

Much remains to be learned about the possibilities of thiols in the treatment of poisoning by various metals. It may well be that other mercaptans may prove safer and more effective than BAL itself. Since it is likely that clinicians will be turning to BAL as a form of treatment of human poisoning by many metals, the experience with cadmium should be borne in mind. It was shown in animals that while the prophylactic administration of BAL eliminated the signs of acute intoxication with cadmium chloride, the animals later succumbed to renal damage in the process of excretion of the cadmium-BAL complex. It is clear from this that great caution is necessary in the application of BAL to poisoning by metals in man and that thorough exploration of the problem relating to any particular metal should be made in animals before BAL is applied in cases of human poisoning.

HARRY GOLD, M.D.

Clinical Studies

Effects of Immobilization upon Various Metabolic and Physiologic Functions of Normal Men*

JOHN E. DEITRICK, M.D., G. DONALD WHEDON, M.D.
and
EPHRAIM SHORR, M.D.
with the technical assistance of
VINCENT TOSCANI *and* VIOLA BUNIAK DAVIS
New York, New York

THERE has been a growing concern in recent years not only over the possible relation of bed rest to a variety of hazardous complications commonly encountered during illness but also as to its optimal use as a therapeutic measure during convalescence. During World War II interest in these problems was heightened by the importance to the armed forces of methods whereby the convalescence and rehabilitation of disabled soldiers might be accelerated. This has led to the initiation of studies designed to clarify the physiologic and metabolic derangements associated with traumatic and infectious states as well as the manner in which they are influenced by bed rest.

The value of the information provided by any such study will depend upon the appreciation of the many factors participating in the reaction of the organism to stress and upon the extent to which differentiation of these factors has been made possible by the conditions under which the observations have been carried out. The complexity of the factors involved is apparent from a consideration of the variety of phenomena which have been attributed to bed rest. These range from the relatively acute pathologic complications such as phlebothrombosis, pulmonary embolism and hypostatic pneumonia to the more chronic pathologic and functional disturbances which include decubitus ulcers, nephrolithiasis, constipation, myasthenia and many metabolic and vascular functional derangements. Their variety suggests a multiple origin, indicating that investigation of any of these phenomena would require exacting analysis of numerous underlying mechanisms. In any investigation of the rôle of bed rest in disease and convalescence, there are many varying conditions which may exert an influence. It is necessary to consider observations in relation to the amount of activity permitted to the patient. In most discussions, bed rest has been a poorly defined term, activity in bed being inadequately described or controlled. It may vary from the complete inactivity of the comatose patient or one with a fractured spine to the constant movement of the patient with Graves' disease. Some attention should also be directed to the phase of the illness and

* From The Department of Medicine, Cornell University Medical College, The New York Hospital and The Russell Sage Institute of Pathology. This investigation was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University Medical College.

duration of bed rest. A differentiation must be made of the effects of other therapeutic agents from the effects of bed rest. Finally, it is necessary to differentiate the derangements which are presented by a patient bedridden by illness from those which might be attributed to bed rest *per se*, that is, from those derangements which would be experienced by a normal healthy person subjected to the same conditions.

There are few published experiments which satisfy these criteria, a circumstance which is largely responsible for the present controversial status of bed rest as a therapeutic measure. This uncertainty, and also the sparsity of factual or quantitative data, is reflected in the numerous recent criticisms of bed rest[1–4] which have led to the present vogue of early postoperative ambulation.[5–9] A review of the available literature disclosed only two experiments which have attempted to differentiate under controlled conditions between the effects of bed rest or immobilization *per se* and the effects of disease. In 1929, Cuthbertson[10] studied a group of normal subjects maintained on constant diets during periods of bed rest of ten to fourteen days. The bed rest was standardized by the use of splints and sandbags. The brevity of both the control periods and the periods of immobilization reduced the value of these experiments. In 1944, Keys[11–13] carried out similar studies in young normal individuals. They were not restrained by splints or casts and, except for short periods, their activity in bed was unrestricted. In addition, their dietary intake was reduced during the periods of bed rest.

The purpose of the present investigation was to obtain quantitative metabolic and physiologic data on the effects of immobilization on normal, healthy individuals and thus to furnish a basis for differentiating the effects of immobilization *per se* from those which might arise from (or be superimposed by) disease or trauma. The experiment was devised in such a manner as to define and keep constant the activity in bed and to exclude or to control carefully other factors such as disease, diet and environment throughout the period of observation.

PROCEDURE

Four normal, healthy men were studied on constant diets before, during, and following a prolonged period of bed rest. Activity in bed was standardized by immobilization of the pelvic girdle and legs in plaster casts. This was done to avoid the variable amount of activity that young healthy subjects lying in bed might exhibit. The study was carried out on the metabolism ward of the New York Hospital and the Russell Sage Institute of Pathology.

The investigation was planned to include metabolic balance studies in nitrogen, calcium and phosphorus and the analysis of the urine for creatine, creatinine, citric acid and 17-ketosteroids. The investigation was further planned to make observations and tests of circulatory, respiratory, muscular and other physiologic functions. Since a complete study of the effects upon each function was impossible, certain tests in each field were selected which might be expected to yield the most pertinent information and indicate the direction which later studies might follow.

The length of the control period was six to eight weeks, the immobilization period six weeks in the first pair of subjects and seven weeks in the second pair. The recovery period in the first pair was four weeks; this was found to be too short and was lengthened to six weeks in the second pair.

During the control period the subjects were active; in addition to being up and about on the metabolism ward, they took exercise in the form of calisthenics one-half hour and swimming one-half hour each day and were taken by an escort on one-hour walks outside the hospital three or four times a week.

During the immobilization period the subjects were placed in bi-valved plaster casts extending from the umbilicus to the toes. They remained in these casts constantly throughout the immobilization period except for the use of the bed pan and for the ergometer and tilt table tests. Time free of the cast averaged thirty to forty minutes daily. (The plaster cast was first applied to a subject during the early "adjustment" phase of the control period and when dry (thirty-six hours) was bi-valved and removed, the subject returning promptly to control activity. The cast was then padded and fitted with ties in prepara-

tion for occupancy during the immobilization phase.)

In the recovery period, the subjects were ambulant on the sixth day and two weeks after coming out of the casts resumed the same level of activity as they pursued in the control period.

The protein intake was set at slightly less than 1.5 Gm. per Kg. body weight and was more than adequate to maintain nitrogen equilibrium during the control periods. Calcium, phosphorus and potassium were kept constant at medium levels. Sodium intake was not kept constant in the first pair of subjects but was in the second pair.

TABLE 1

DAILY DIETARY INTAKE AND PHYSICAL CHARACTERISTICS OF SUBJECTS

Subject	Age	Height, Cm.	Weight, Kg.	Calories, Daily Intake	Protein, Gm.	Fat, Gm.	CHO, Gm.	Ca, Gm.	P, Gm.	Na, Gm.	K, Gm.
E. M.	29	177	66	2,500	85	110	292	0.852	1.50	....	3.15
C. O.	20	179.5	62	2,800	90	114	352	0.920	1.64	....	3.76
A. S.	25	161	60	2,800	90	114	352	0.920	1.64	4.00	3.76
S. W.	20	181	64	2,800	90	114	352	0.920	1.64	4.00	3.76

The first pair of subjects was studied from August to December, 1944, and the second pair from February to June, 1945.

Subjects. Conscientious objectors volunteered as subjects for this experiment and were transferred to the hospital by Selective Service. They were healthy young men, varying in age from twenty to twenty-nine years. Physical characteristics of age, height and weight are listed in Table 1.

The subjects differed considerably in body type. E. M. was of medium height and moderately muscular. A. S. was a Nisei, rather short and of excellent muscular development. C. O. and S. W. were rather tall and slender. The only physical defect in the group was found in S. W. who had an accentuated first heart sound at the mitral area, pulmonic second sound louder than aortic second sound and on exercise a short, rolling, crescendo, presystolic murmur at the mitral area. However, his heart was not enlarged, the left auricle did not compress the esophagus, the electrocardiogram was normal and the heart showed excellent reserve power.

Diets. The diets (Table 1) were selected at such levels that they could be kept constant throughout all periods of the experiment. They were calculated to maintain the subjects in caloric, mineral and nitrogen balance during the control periods, yet permit complete ingestion during immobilization. One subject (E. M.) received 2,500 calories; the other three, 2,800 calories. The diets were not creatine-creatinine free and for each of the diets there were actually three daily menus which were rotated in succession.

Calculated values for the caloric and mineral content of the various foods were obtained largely from the sixth edition of Sherman.[14] Values for grapejuice were obtained from the fourth edition of Sherman, for rye bread from Rose[15] and for cereals from McCance and Widdowson.[16]

A total of twelve diet analyses (*in toto* method) was carried out during the course of the studies. The average percentage of the calculated values recovered by analysis was 96.5 per cent for nitrogen, 98.2 per cent for calcium and 93.1 per cent for phosphorus. In the balance studies of these three elements the calculated values were taken as the intake. For potassium, 83.7 per cent of the calculated values was recovered on analysis of the diets and for sodium 108.3 per cent was recovered on analysis as compared with the calculated values. Since the tables used to obtain the sodium and potassium content of foods were incomplete and of questionable validity, the values we obtained by analysis were used as the intake for the balance studies of these two elements. (When tables later became available giving the sodium and potassium content of foods based on analyses made by the flame photometer,[17] recalculation of the contents of the diets when compared with the diet analyses revealed that the average percentage of the calculated values recovered on analysis was 89.3 per cent for potassium and 99.8 per cent for sodium.) In the second pair of subjects (A. S. and S. W.), the sodium intake was kept constant at 4.0 Gm. per day by giving measured

amounts of sodium chloride to be sprinkled over the food.

Methods. A. Chemical studies: A general description of the ward routine and methods employed on the metabolism ward of the Russell Sage Institute of Pathology and the New York Hospital has been given by E. F. DuBois.[18,19]

The measured diets and collection of specimens for the chemical balance studies were begun the day after the subjects' arrival on the ward. It was found that it took from one week to ten days for adjustment to the diet and ward routine as judged by the establishment of relative stability in the day to day output of chemical constituents.

The metabolic balance studies were carried out in seven-day periods. Fecal nitrogen, calcium, phosphorus, sodium and potassium were determined by chemical analysis. Urinary calcium, phosphorus and citric acid were determined daily in the first two subjects studied and on four- and three-day pooled specimens in the subsequent studies. Urinary sodium, potassium, inorganic sulfur and 17-ketosteroids were determined on seven-day pooled specimens.

Urine specimens were preserved by refrigeration and the addition of 20 cc. of toluol to each twenty-four-hour collection. To the seven-day pooled specimens, made up of aliquots of the twenty-four-hour collections, was added 10 cc. of concentrated HCl.

Stool specimens were collected in individual covered enameled containers which were kept in the ice box. The stool periods were marked by giving by mouth 0.2 Gm. carmine at 9 P.M. on the last day of the period. Stool specimens were evaporated to dryness, weighed, ground and completely mixed. (Drying of a stool was begun within one day of the time it was passed in order to prevent decomposition.)

Diets were analyzed *in toto*, one day's entire menu being mixed together, ground and then prepared for analysis in the same manner as in the preparation of a stool for analysis. Blood was drawn for analysis when the subjects were in the fasting, basal state. Specimens were allowed to stand at room temperature for two hours, then centrifuged twice and the serum withdrawn.

Urine and stool specimens were analyzed for nitrogen by a modification of the Kjeldahl method;[20] for stool nitrogen analysis an aliquot of the dry stool was placed directly in a Kjeldahl flask. Urine and stool specimens were analyzed for phosphorus by the method of Fiske and Subbarow.[21] Calcium in the urine was determined by the method of Shohl and Pedley;[22] the preparation of stool for calcium analysis was carried out as outlined in Hawk and Bergeim[23] and the neutralization and analysis by the method of Shohl and Pedley.[22] The creatine content of the urine was determined by the method of Benedict;[24] creatinine by the method of Folin;[25] citric acid by the method of Taussky and Shorr[26] and total sulfate (inorganic and ethereal) sulfur by the method of Folin.[27] Urine pH was determined in a Hydrogen Ion Concentration Meter. The excretion of 17-ketosteroids in the urine was determined by a modification[28] of the method of Callow, Callow and Emmens;[29] the ketosteroids were hydrolyzed and extracted (three times) by shaking with carbon tetrachloride at room temperature; the extract was cleared of estrogens with sodium hydroxide and water and the final extract prepared according to the original method. Sodium and potassium in serum, urine and stool were determined by a flame photometer, designed by Barnes, Richardson, Barry and Hood[30] and the analyses carried out by the methods of Hald[31] and Toscani and Buniak.[32] The sodium and potassium analyses of the blood were determined on diluted samples of serum and analyses of urine on diluted urine specimens; the analyses of food and stool were carried out upon weakly acidified solutions of ash prepared in the same manner as for calcium analysis.[23] Serum specimens were analyzed for calcium by the method of Clark and Collip,[33] phosphorus by the method of Fiske and Subbarow[21] and total proteins by the Kjeldahl method.[20] Blood prothrombin levels were determined by a modification of the method of Herbert.[34]

Creatine tolerance tests[35,36] were performed in the following manner: Since the diets were not creatine-free, the subjects were given the same menu for three successive days. On the second of the three days, the subjects were given 1.32 Gm. of creatine hydrate at 10 A.M. The test dose of creatine hydrate, 1.32 Gm., is equivalent to 1.0 Gm. of creatine in the urine expressed as creatinine. The control creatine excretion was taken as the average of the first day's excretion and the excretion of the two days in the preceding week upon which the subject received the same menu as during the test days. Calculation of the percentage of fed creatine retained, i.e., the creatine tolerance, was based on the total excretion of the day of and the day follow-

ing the administration of the test dose of creatine. From the excretion of each of these two days the control excretion was subtracted. The difference represented that fraction of the ingested creatine which was not retained. This figure, when divided by the total amount of creatine which might have been excreted (1.0 Gm.) from the test dose, represented the per cent excreted. Subtracting this figure from 100 per cent yielded as a result the percentage of fed creatine retained. The minimum normal value for creatine tolerance is 70 per cent.

Biologic assay of adrenal corticosteroids in the urine by the determination of the amount of glycogen deposited in the liver of adrenalectomized mice[37] was carried out for us by Dr. Konrad Dobriner of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York. The determinations were made on two subjects, E. M. and C. O., on seven-day pooled specimens during the last four control weeks and during the immobilization and recovery periods.

B. Physiological studies: Subjects were weighed daily during the control and recovery periods. During immobilization they were weighed twice weekly in the casts on a weighing table, the weight of the cast and the table being subtracted. The basal metabolic rate was determined weekly by the method of Benedict and Roth.[38]

Muscle power was measured every four to eight days during the control periods and every ten days during the immobilization and recovery periods on an ergometer, a modification of the ergograph designed by Co Tui.[39] The ergometer differs from the Co Tui ergograph in being fitted with a Kirstei adjustable Thomas splint and a Chatillon spring scale against which the subject pulled. The ergometer was designed to test muscle groups in all four extremities with the subject supine: (a) the biceps group in the flexed arm pull (elbow at 90 degrees); (b) the shoulder and arm muscles in the straight arm pull; (c) the anterior tibial group in the foot pull (leg straight) and (d) the gastrocnemius-soleus group in the foot push. Muscle power was taken as the number of pounds pull (best one of three) from the spring scale; there was a two-minute rest between each pull in order to avoid fatigue. Strength of grip was measured on a hand dynamometer. Studies of the rate of muscular fatigue were attempted in several ways but it was found that motivation played too great a rôle and the studies were therefore discontinued. (For the ergometer tests during the immobilization period (every ten days) the subject slept out of the cast the night preceding the test to lessen muscle and joint stiffness, then the subject was put back in the cast in the early afternoon after an average of eighteen hours out of the cast.)

Girth of the upper and lower arms, thighs and calves were measured at standard distances from bony prominences twice weekly in the first pair of subjects, using a narrow, steel tape measure. In an effort to overcome the source of error resulting from variable tension on the tape measure, a device was made consisting of an encircling 1½ inch wide metal band, with tape measure rivited along one edge; the band was mounted on a standard in such a way that 2 (and 5) pound weights could be hung from the metal band's free end in order to produce a constant tension. With this device (used for the measurement of calf and thigh circumference on the second pair of subjects), measurements of the circumference of the calf could be closely checked by different observers (standard deviation over four control weeks equaled ±2.4 mm. or 0.67 per cent.) Measurements were made after subjects had been lying down not less than thirty minutes in order to measure the leg when in a constant state. Measurements of the circumference of the legs showed a gradual decline over the first thirty to forty minutes after the assumption of the horizontal position before reaching measurements approximating those found in the morning basal state.

The reaction of the circulation to the upright position in prolonged motionless standing was studied by the tilt table test which has enjoyed increasing favor in recent years as a measure of the "fitness" of the circulatory system.[40–42] The subject lay quietly in the horizontal position on the tilt table for twenty-five to forty minutes during which pulse rate and blood pressure readings were taken every two to four minutes. The pulse rate and blood pressure usually became well stabilized within twenty minutes. The table was then tilted slowly over a period of thirty seconds to an angle of 65 degrees, feet down, the subject adjusting his feet on the footboard at that time if necessary; thereafter, the subject stood motionless and unsupported with arms at his side, his weight being borne mainly by his heels against the footboard. Pulse rate and blood pressure readings were made every one to two minutes with the subject in this position. The subject remained in the tilted position for

twenty minutes, unless fainting occurred in a shorter interval. During a number of tilt table tests electrocardiograms (three standard leads) and measurements of the girth of the right calf and thigh were taken before, during and following tilting. During the immobilization period

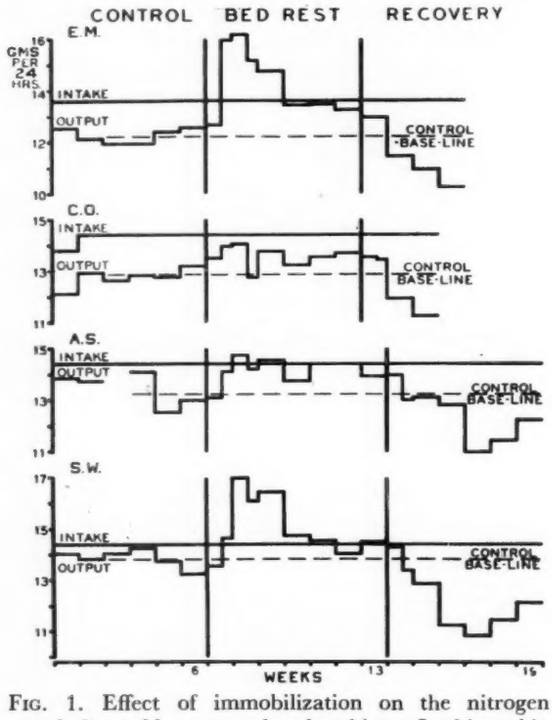

FIG. 1. Effect of immobilization on the nitrogen metabolism of four normal male subjects. In this and in each of the subsequent graphs "bed rest" indicates the immobilization phase. For each subject the control base-line is an average of the total outputs of the last four control weeks. The nitrogen outputs of the first two weeks of immobilization and of the first recovery week have been charted in four- and three-day periods in order to indicate the duration of the delay in the increase in nitrogen excretion during immobilization, the peak of nitrogen excretion during immobilization and the delay in the fall in nitrogen excretion during recovery.

the subjects were taken out of their casts thirty minutes prior to the test. Tests were performed at the same time of day (3 P.M.) and under relatively constant temperature conditions.

Blood volume determinations were made employing the Evans blue (T-1824) method of Gregersen, Gibson and Stead[43] as outlined by Gibson, Evans and Evelyn.[44,45] Hematocrits were determined by the Wintrobe tube, and centrifugation was carried out for sixty minutes at 3,000 r.p.m. Hematocrits were corrected by allowing 8.5 per cent for the per cent of the observed cell volume as plasma trapped between red cells.[46] A dye standard was prepared for each blood volume determination from the ampule of dye used for injection. Possible hemolysis in the serum samples containing dye was corrected by the formula of Gibson and Evelyn.[45]

At the time of withdrawal of blood for the serum blank, blood was also withdrawn for coagulation time determinations by the method of Lee and White. Test tubes of Wassermann tube size (1.1 cm. diameter) were used which give coagulation times in normals that are somewhat longer than those obtained with the standard tube 8 mm. in diameter.[47] Coagulation times of the subjects during the control periods were eight to eleven minutes. At the conclusion of the blood volume determinations circulation times were measured, employing decholin and macasol.[48]

The Master two-step test[49] and the Schneider test[50,51] were used as indices of physical fitness. Using the Master test in the first subject E. M., the maximum number of climbs was determined following which the pulse rate and systolic blood pressure returned to within ten points of the resting level within two minutes; in the other three subjects, the number of climbs was kept constant for each subject and the varying response of pulse and systolic pressure noted. The Schneider index was selected because it can be performed without undue effort by a convalescent able to stand and step up on an 18-inch step. As often as possible, tests were performed at the same time of day (4 P.M.).

Tests of respiratory function included vital capacity, ventilation at rest per minute and maximum ventilation capacity per minute[52] employing a calibrated 85 liter capacity Tissot gasometer. Ventilation per minute at rest was taken as the average of two, five-minute periods under basal conditions. Maximum ventilation capacity per minute was taken as the average of two, thirty-second runs. Determinations were also made of breath-holding time and of the behavior of the pulse during breath-holding against a 40 mm. column of mercury (Flack or "persistence" test[53,54]).

X-rays of the long bones and spine of the first pair of subjects were made at intervals under exactly duplicated x-ray technic in an effort to detect possible bone rarefaction resulting from immobilization.

Observations were made of the resting pulse rate and blood pressure before, during and following immobilization. Measurements made during tests carried out in the morning basal

state make up a large proportion of the data of this comparative study.

RESULTS

A. Chemical Studies. 1. *Nitrogen:* (Fig. 1.) During the control periods the subjects maintained small positive nitrogen balances with the output relatively constant. The total outputs of the last four control periods were averaged to obtain the control base line. This is drawn on the graph as an interrupted line to demonstrate clearly the deviations of nitrogen excretion during the immobilization and recovery periods from that of the control period. Each subject established his own distinctive balance with respect to intake so that in assessing the effect of immobilization upon nitrogen excretion, displacements from a control base line are of greater significance than balances related to intake. Displacements or variations from the control base line have been employed for the calculation of total losses throughout the nitrogen and mineral balance studies.

During immobilization all four subjects showed an increase in nitrogen excretion which was reflected principally in the urinary nitrogen. The fecal nitrogen remained relatively constant throughout all phases of the experiment. During the first four days of immobilization there was little change in the output; a rather abrupt rise then occurred generally on the fifth or sixth day. This delay (Table II) of four or five days is in contrast to the immediate excessive excretion of nitrogen in response to fever and the delay of only one day following trauma. The peak of nitrogen excretion occurred during the second week. The extent of nitrogen loss varied considerably

TABLE II

DELAY IN THE INCREASE IN NITROGEN EXCRETION DURING IMMOBILIZATION; DAILY URINARY NITROGEN AND DAILY TOTAL (URINARY PLUS FECAL) NITROGEN EXCRETION DURING FIRST TEN DAYS OF IMMOBILIZATION

	Subject E. M.		Subject C. O.		Subject A. S.		Subject S. W.	
	Urinary N, Gm.	Total N, Gm.	Urinary N, Gm.	Total N, Gm.	Urinary N, Gm.	Total N, Gm.	Urinary N, Gm.	Total N, Gm.
Average of last four control weeks...	11.35	12.21	11.59	12.87	11.45	13.24	12.68	13.82
Average deviation of daily output from average of last four control weeks.....	±0.90	.....	±0.76	.....	±0.65	.....	±0.64	
Immobilization period								
Day 1.....	13.65*	14.54*	12.60	13.89	10.53	12.61	11.90	12.97
2.....	11.69	12.58	12.35	13.64	10.80	12.88	12.88	13.95
3.....	11.37	12.26	12.50	13.79	11.30	13.38	12.72	13.79
4.....	12.70	13.59	11.45	12.74	11.50	13.58	12.50	13.57
5.....	*15.89*†	*16.78*	11.42	12.71	11.80	13.88	10.99	12.06
6.....	13.60	14.49	*14.20*	*15.49*	12.03	14.11	*13.82*	*14.89*
7....	15.70	16.59	12.42	13.71	12.25	14.33	15.70	16.77
8.....	15.30	16.42	12.18	13.39	*13.20*	*14.91*	16.02	17.18
9.....	16.20	17.32	11.95	13.16	12.75	14.46	14.85	16.01
10.....	14.90	16.02	14.20	15.41	13.79	15.50	16.95	18.11

* High urinary creatinine on this day and low creatinine on preceding day suggests that this represents more than a twenty-four-hour sample.

† Figures in italics indicate the first day of significant increase in nitrogen excretion.

in the several subjects and could not be correlated with body type. During the recovery phase nitrogen excretion remained high for a few days and then fell rapidly to reach the control level by the second week. The output continued to decrease, falling below control levels so that nitrogen was then being stored. Maximum storage or retention occurred at the fourth recovery week. In the two subjects studied for six weeks in recovery, nitrogen excretion was again approaching control levels by the end of the sixth week.

The total nitrogen losses during immobilization ranged from 29.8 Gm. to 83.6 Gm. (Table III.) The average of the total nitrogen losses among the four men was 53.7 Gm., equivalent to 1.7 Kg. of muscle protoplasm.

2. *Calcium:* During the control periods the subjects remained in positive calcium balance. During immobilization there was an increase in both urinary and fecal calcium excretion. The increase in fecal calcium excretion was variable but generally progressive, fecal calcium being greatest during the latter weeks of bed rest.

Urinary calcium excretion began to increase on the second or third day of bed rest, that is, slightly preceding the increase in nitrogen excretion, and climbed gradually, reaching a peak by the fourth to fifth week. This high level of urinary excretion

TABLE III

NITROGEN METABOLISM—TOTAL NITROGEN LOSSES DURING IMMOBILIZATION, TOTAL RETENTION DURING RECOVERY AND MAXIMUM DEVIATION FROM CONTROL BASE-LINE (AVERAGE OF LAST FOUR CONTROL WEEKS)

I. Immobilization

Subject	Control	Immobilization Period							
								Maximum Deviation from Control Base-line	
	Average Daily Balance (last 4 wk.), Gm.	No. of Wk.	Average Daily Balance, Gm.	Average Daily N Loss, Gm.	Total N Loss (entire period), Gm.	Total N Loss (first 2 wk.), Gm.	Total N Loss (first 3 wk.), Gm.	Week of Occurrence	Deviation, Gm./day (for the week)
E. M.	+1.36	6	−0.63	1.99	83.6	40.3	58.3	2nd	−3.55
C. O.	+1.54	6	+0.83	0.71	29.8	10.3	16.7	3rd	−0.91
A. S.	+1.18	7	+0.25	0.93	45.6	11.0	20.2	3rd	−1.32
S. W.	+0.60	7	−0.54	1.14	55.9	20.7	38.4	2nd	−2.78

II. Recovery

Subject	No. of Weeks	Average Daily Balance, Gm.	Average Daily N Gain, Gm.	Total N Retention, Gm.	Maximum Deviation from Control Base-line	
					Week of Occurrence	Deviation, Gm./day (for the week)
E. M.	4	+2.15	0.79	22.1	4th	+1.95
C. O.	3	+2.18	0.64	13.4	3rd	+1.63
A. S.	6	+2.05	0.87	36.5	4th	+2.24
S. W.	6	+2.34	1.74	73.1	4th	+2.97

was more than double the control period levels in all four subjects and was maintained in a more or less plateau manner similar to that described by Howard[55] in patients with fractures. The maximum excretion in the urine ranged from 140 to 594 mg. per day (for a three to four-day pool) with an average maximum of 342.

Calcium excretion (urinary and total) decreased slowly in recovery, continuing to exceed control levels during the first three weeks. Calcium excretion continued to decrease thereafter, minimum excretion occurring during the fifth and sixth recovery weeks in the two subjects studied for this length of time. Subject S. W. exhibited marked calcium retention during the fifth and sixth weeks in recovery and had not returned to control levels at the end of the sixth week.

The pattern and extent of the calcium changes are shown in Figure 2 and Tables IV and V. Total calcium losses ranged from 8.95 to 23.9 Gm. and averaged 14.1 Gm. (These calculations include the first three recovery weeks since calcium excretion still exceeded control levels during that time.)

Among the factors that influence the solubility of urinary calcium are urine volume, urinary pH and urinary citric acid concentration. The importance of the dilution factor and of acidity of the urine in favoring calcium solubility is well recognized. The significance of urinary citric acid has been more recently appreciated; this influence resides in the formation of the weakly ionized and very soluble calcium citrate complex. Some evidence for the protective action of citric acid has been shown by Shorr, Almy, Sloan, Taussky and Toscani[56] in ambulatory patients in whom

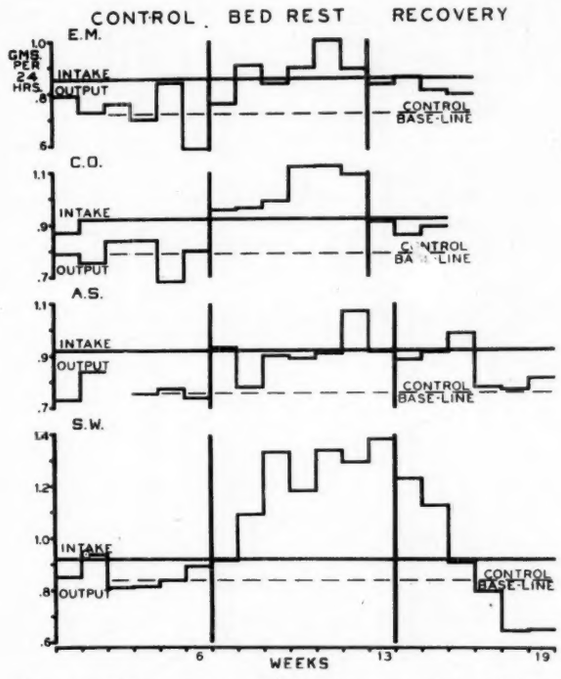

FIG. 2. Effect of immobilization on the calcium metabolism of four normal male subjects.

TABLE IV

CALCIUM METABOLISM—TOTAL CALCIUM LOSSES RESULTING FROM IMMOBILIZATION AND MAXIMUM DEVIATION FROM CONTROL BASE-LINE (AVERAGE OF LAST FOUR CONTROL WEEKS)

Subject	Control	Immobilization						Recovery	
	Average Daily Balance, (last 4 wk.), Gm.	No. of Wk.	Average Daily Balance, Gm.	Average Daily Ca Loss, Gm.	Total Loss in Immobilization, Gm.	Maximum Deviation from Control Base-line		Additional Ca Loss (first 3 wk.), Gm.	Total Calcium Loss, Gm.
						Week of Occurrence	Deviation, Gm./day (for the wk.)		
E. M.	+0.131	6	−0.028	0.159	6.68	5th	−0.280	2.27	8.95
C. O.	+0.130	6	−0.118	0.248	10.42	5th	−0.329	2.04	12.46
A. S.	+0.162	7	+0.006	0.156	7.65	6th	−0.312	3.59	11.24
S. W.	+0.081	7	−0.299	0.380	18.62	7th	−0.543	5.25	23.87

TABLE V

CHANGES IN URINARY CALCIUM EXCRETION RESULTING FROM IMMOBILIZATION

Subject	Control	Immobilization						
	Control Base-line Urinary Calcium, Gm./day	No. of Wk.	Average Daily Urinary Calcium, Gm.	Average Daily Urinary Calcium Loss (above control base-line), Gm.	Total Urinary Calcium Loss (above control base-line), Gm.	Maximum Urinary Calcium		
						Wk. of Occurrence	Maximum for Week, Gm./day	Deviation from Control Base-line, Gm./day
E. M.	0.050	6	0.102	0.052	2.18	4th	0.119	0.069
C. O.	0.116	6	0.284	0.168	7.06	6th	0.335	0.219
A. S.	0.123	7	0.212	0.089	4.36	6th	0.249	0.126
S. W.	0.213	7	0.515	0.302	14.80	5th	0.577	0.364

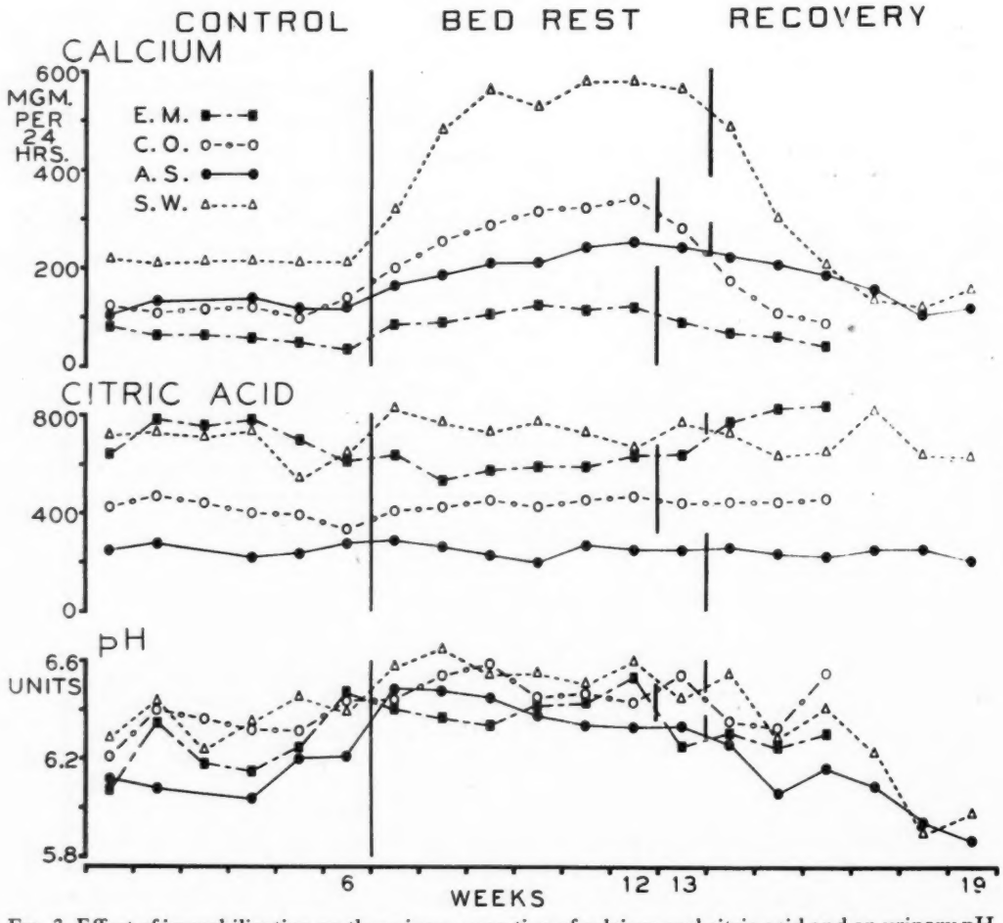

FIG. 3. Effect of immobilization on the urinary excretion of calcium and citric acid and on urinary pH in four normal male subjects. Daily calcium intake was 0.852 Gm. for subject E. M., 0.920 Gm. for subjects C. O., A. S. and S. W.

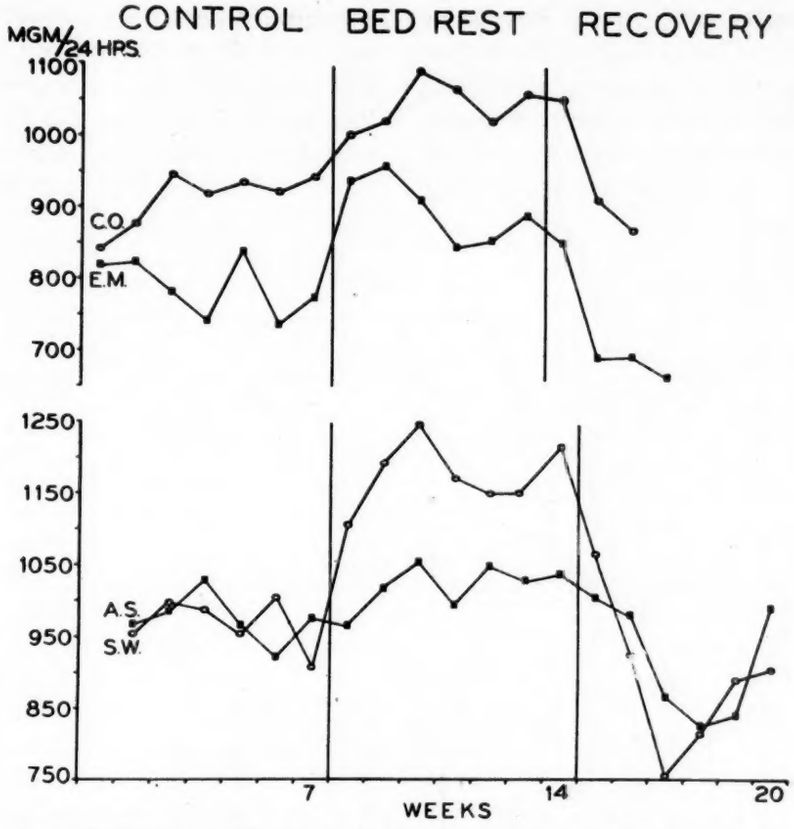

FIG. 4. Effect of immobilization on the urinary excretion of phosphorus of four normal male subjects. Daily phosphorus intake was 1.50 Gm. for subject E. M., 1.64 Gm. for subjects C. O., A. S. and S. W.

variations in calcium excretion are paralleled by proportional variations in the excretion of citric acid.

Despite the fact that urinary calcium levels were doubled, factors influencing urinary calcium solubility showed little or no change. During immobilization urine volumes increased only slightly, the average daily urine volumes averaging 235 cc. higher during immobilization than during the control period. The urinary pH rose between 0.1 and 0.2 units during immobilization. The citric acid excretion failed to show any compensatory rise. (Fig. 3.) No red blood cells or calcium phosphate crystals were found in frequent microscopic examinations of the urines.

3. *Phosphorus:* During the control periods the subjects remained in positive phosphorus balance. During immobilization there was an increase in both urinary and fecal phosphorus excretion, the increase in fecal phosphorus being small and variable. Urinary phosphorus excretion (Fig. 4) began to increase during the first week of immobiliza-

TABLE VI

PHOSPHORUS METABOLISM—TOTAL PHOSPHORUS LOSSES RESULTING FROM IMMOBILIZATION AND MAXIMUM DEVIATION FROM CONTROL BASE-LINE (AVERAGE OF LAST FOUR CONTROL WEEKS)

Subject	Control	Immobilization					
	Average Daily Balance (last 4 wk.), Gm.	No. of Weeks	Average Daily Balance, Gm.	Average Daily Loss, Gm.	Total Loss in Immobilization, Gm.	Maximum Deviation from Control Base-line	
						Week of Occurrence	Deviation, Gm./day (av. for the wk.)
E. M.	+0.328	6	+0.058	0.270	11.34	2nd	−0.373
						5th	−0.319
C. O.	+0.278	6	+0.145	0.133	5.60	4th	−0.188
A. S.	+0.245	7	+0.129	0.116	5.69	3rd	−0.125
						6th	−0.243
S. W.	+0.169	7	−0.070	0.239	11.70	3rd	−0.370
						7th	−0.356

tion and reached a peak at the second to third week; this peak coincided rather closely with the peak of nitrogen excretion. Urinary phosphorus then decreased somewhat but demonstrated a second peak of excretion at the sixth to seventh week. This second peak occurred at a time when calcium excretion was at its highest level. In recovery, urinary phosphorus fell rapidly and phosphorus retention took place during the third, fourth and fifth recovery weeks. Excretion returned to control levels in the sixth recovery week.

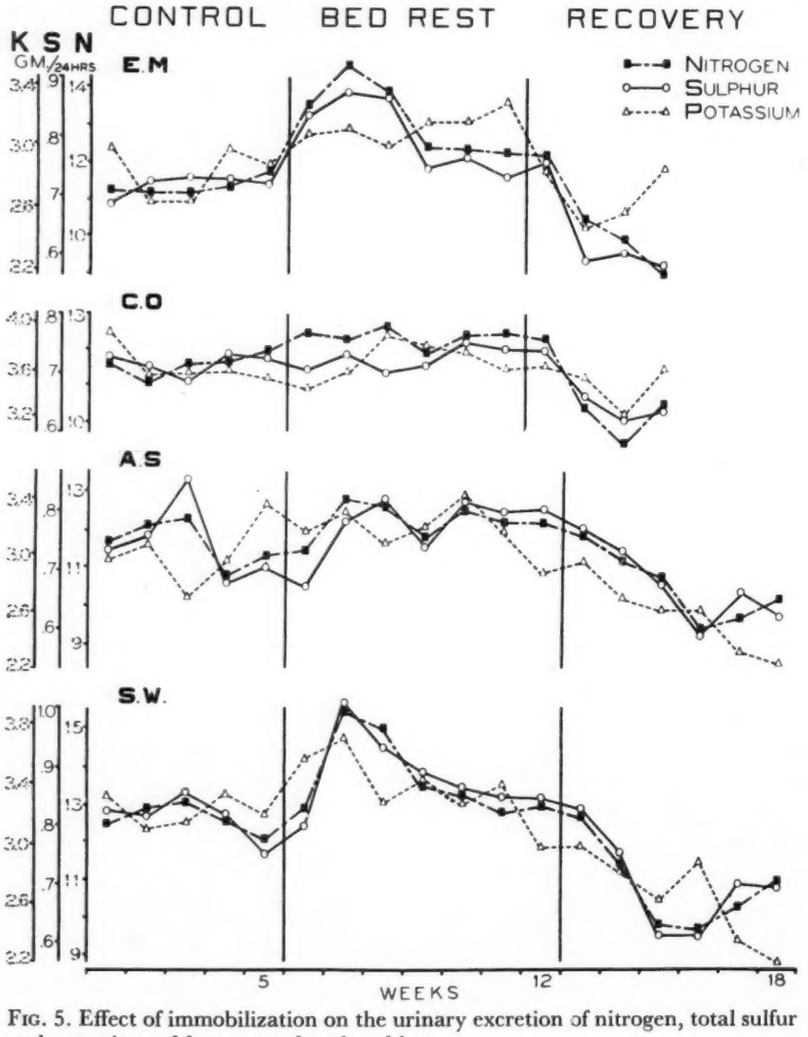

FIG. 5. Effect of immobilization on the urinary excretion of nitrogen, total sulfur and potassium of four normal male subjects.

Total phosphorus losses ranged from 5.6 to 11.6 Gm. (Table VI.) Discrepancies between theoretical phosphorus losses (calculated from nitrogen and calcium) and measured phosphorus losses in each subject were as follows: The theoretical phosphorus loss exceeded the measured phosphorus loss by 19.5 per cent for C. O., 14.5 per cent for A. S. and 5.1 per cent for S. W.; for E. M. the theoretical phosphorus loss was 23.4 per cent less than the measured loss. There was fairly good agreement from week to week between measured and theoretical phosphorus losses.

4. *Total sulfur:* The average ratio of urinary total sulfur to urinary nitrogen in the four subjects during the last five control weeks was 1:15.8. This ratio of sulfur to nitrogen was maintained quite constantly throughout the immobilization and recovery periods. (Fig. 5 and Table VII.)

The sulfur in these ratios is slightly less than in the generally accepted sulfur-nitrogen ratio of muscle of 1:14. However, the close correlation of the sulfur excretion with nitrogen from week to week during immobilization suggests a sulfur-rich source of the excreted nitrogen, presumably muscle.

was only 5 to 8 per cent and the day to day coffee intake was quite constant.

During the control period the subjects were approximately in potassium equilibrium. During immobilization potassium excretion increased, total losses based on variations from control base line excretion

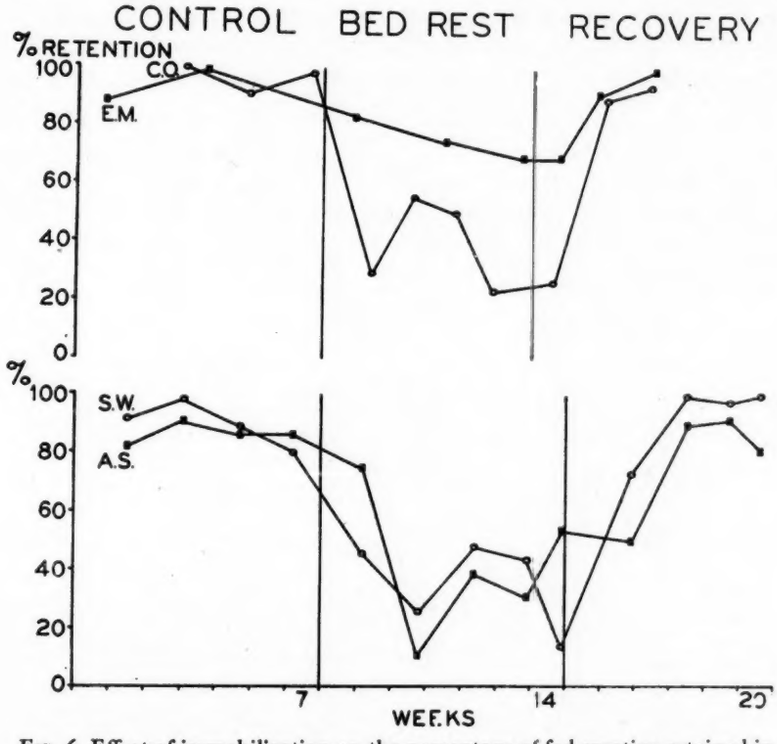

FIG. 6. Effect of immobilization on the percentage of fed creatine retained in creatine tolerance tests in four normal male subjects. The test dose of creatine was 1.32 Gm.

5. *Potassium:* Potassium balance data were not strictly accurate because of minor variations in the daily potassium intake. The discovery that ordinary beverage coffee contains appreciable amounts of potassium (89 mg. per 100 cc. by our analysis, 88 mg. per 100 cc. by McCance and Widdowson[16] in a five-minute infusion), made it evident that the daily intake was actually 200 to 300 mg. higher than was indicated from the diet analyses. This additional potassium intake from coffee was estimated to be 0.25 Gm. and this value was added to the potassium intake figures. The general conclusions regarding the effect of immobilization upon potassium metabolism are believed not to be invalidated because the increase in potassium intake from coffee ranging from 4.2 to 14.2 Gm. The increase in potassium excretion occurred only in the urine (Fig. 5), fecal potassium remaining unchanged. In recovery, all four subjects developed positive potassium balances and in the two subjects studied for six weeks in recovery, potassium balances were still strongly positive at the sixth week. The total amounts of potassium retained by these two subjects in six weeks recovery more than doubled the amounts they lost during immobilization.

6. *Sodium:* Sodium balances were carried out on the second pair of subjects. The total sodium excretion was slightly increased during immobilization and fell slightly below control levels during recovery. The principal change occurred in urinary sodium;

actually, the amounts of sodium in the feces (which were less than 0.2 Gm. daily) tended to be reduced during immobilization.

In the first subject (A. S.), the sodium balance was +0.46 Gm. per day during control, shifted to +0.17 during immobilization and to +0.71 in recovery. In the second subject (S. W.), sodium balance was +0.16 Gm. per day in control, −0.02 during immobilization and +0.34 in recovery.

7. *Creatine metabolism:* Urinary creatinine excretion remained quite constant throughout all periods of study. There were day to day fluctuations at a low level in creatine excretion (dietary intake was not creatine-free) but no significant shifts occurred from one period of study to the next. However, tests of creatine tolerance showed a considerable fall during immobilization. (Fig. 6.) All control period tests showed greater than 80 per cent retention (well within the normal range). During immobilization there was a gradual fall in retention, the minimum ranging from 11 to 70 per cent with an average minimum retention of 29 per cent. During recovery the tests gradually improved and reached normal levels at the end of the third week.

8. *17-ketosteroids:* Changes in 17-ketosteroid excretion varied considerably from subject to subject. (Table VIII.) One subject (E. M.) showed a variable fall in 17-ketosteroids during immobilization which appeared to be significant. Two subjects (C. O. and S. W.) showed small increases during immobilization. The increase in

TABLE VII

RATIO OF URINARY NITROGEN TO URINARY TOTAL SULFUR

Periods	Subject E. M.			Subject C. O.			Subject A. S.			Subject S. W.		
	Av. Daily Urinary Nitrogen, Gm.	Av. Daily Urinary Total S, Gm.	N:S Ratio	Av. Daily Urinary Nitrogen, Gm.	Av. Daily Urinary Total S, Gm.	N:S Ratio	Av. Daily Urinary Nitrogen, Gm.	Av. Daily Urinary Total S, Gm.	N:S Ratio	Av. Daily Urinary Nitrogen, Gm.	Av. Daily Urinary Total S, Gm.	N:S Ratio
Control—last four weeks	11.12	.724	15.38	11.20	.708	15.83	.....	....	.....	12.84	.815	15.76
	11.11	.733	15.16	11.57	.685	16.89	12.31	.854	14.42	13.08	.856	15.29
	11.36	.726	15.66	11.68	.720	16.23	10.73	.683	15.70	12.68	.815	15.56
	11.79	.721	16.34	11.92	.725	16.46	11.32	.705	16.07	12.10	.750	16.12
Average of control weeks	11.35	.726	15.64	11.59	.710	16.35	11.45	.747	15.40	12.67	.809	15.68
Immobilization												
1st wk	13.51	.837	16.17	12.42	.707	17.58	11.46	.673	17.03	12.93	.798	16.21
2nd wk	14.62	.877	16.68	12.29	.731	16.80	12.80	.783	16.34	15.44	1.010	15.30
3rd wk	13.86	.875	15.84	12.57	.698	18.00	12.70	.816	15.57	15.04	.933	16.12
4th wk	12.44	.747	16.67	11.97	.711	16.84	11.83	.740	16.00	13.56	.887	15.30
5th wk	12.37	.765	16.17	12.38	.753	16.43	12.68	.817	15.52	13.30	.857	15.52
6th wk	12.32	.732	16.83	12.47	.740	16.86	12.21	.796	15.34	12.70	.848	14.98
7th wk	.....	....	.....	.....	....	.....	12.18	.805	15.13	13.04	.843	15.48
Recovery												
1st wk	12.04	.757	15.92	12.33	.738	16.72	11.87	.768	15.44	12.68	.829	15.30
2nd wk	10.49	.590	17.78	10.38	.662	15.70	11.22	.733	15.33	11.47	.753	15.24
3rd wk	9.96	.605	16.47	9.45	.622	15.20	10.78	.680	15.84	9.81	.610	16.06
4th wk	9.07	.580	15.62	10.46*	.636	16.44	9.32	.593	15.69	9.62	.612	15.72
							9.69	.663	14.60	10.28	.700	14.70
							10.22	.620	16.52	10.99	.693	15.86

* 4 days.

S. W. is probably significant; in C. O. it is questionable. The fourth subject (A. S.) showed a fairly constant 17-ketosteroid excretion throughout the experiment. During recovery no significant changes took place other than a gradual return to control levels of excretion.

variation in the excretion values throughout the study and by the irregular appearance of equally high peaks of excretion during both the control and immobilization phases. There was no apparent correlation between the excretion of glycogenic corticoids and nitrogen or 17-ketosteroids.

TABLE VIII

URINARY 17-KETOSTEROID EXCRETION (ANALYSES OF SEVEN-DAY POOLED URINE SPECIMENS) AND COMPARISON WITH TOTAL NITROGEN EXCRETION

Periods	Subject E. M.		Subject C. O.		Subject A. S.		Subject S. W.	
	17-Keto-steroids, mg./day	Nitrogen Total Excretion, Gm./day	17-Keto-steroids, mg./day	Nitrogen Total Excretion, Gm./day	17-Keto-steroids, mg./day	Nitrogen Total Excretion, Gm./day	17-Keto-steroids, mg./day	Nitrogen Total Excretion, Gm./day
Control—last six weeks	9.50	12.52	11.70	12.13	.....	13.86	.....	14.03
	11.00	12.13	9.62	12.92	8.85	13.75	8.10	13.82
	10.98	11.95	9.80	12.66	.....	.....	9.65	14.04
	10.90	11.94	9.85	12.82	9.55	14.13	8.82	14.27
	11.90	12.39	10.10	12.78	9.27	12.55	9.20	13.74
	10.65	12.55	9.52	13.23	9.90	13.04	10.70	13.22
Average of last four control weeks	11.11	12.21	9.82	12.87	9.57	13.24	9.59	13.82
Immobilization								
1st week	9.88	14.40	9.26	13.71	10.32	13.54	10.01	14.00
2nd week	8.55	15.74	10.90	13.50	10.34	14.51	12.39	16.60
3rd week	8.95	14.77	12.25	13.79	9.85	14.56	12.10	16.35
4th week	6.02	13.45	10.05	13.23	9.42	13.75	11.45	14.74
5th week	10.50	13.47	12.32	13.56	8.12	14.43	11.30	14.52
6th week	7.10	13.27	11.88	13.73	9.40	14.43	11.90	14.02
7th week	.....	.....	.....	.....	9.22	13.93	12.10	14.48
Average of immobilization period	8.50	14.18	11.11	13.59	9.52	14.16	11.61	14.96
Recovery								
1st week	7.44	12.94	10.14	13.51	8.83	13.59	11.97	13.90
2nd week	9.16	11.46	9.77	11.96	9.25	13.09	9.70	12.86
3rd week	9.50	10.95	10.40	11.25	10.98	12.79	10.50	11.24
4th week	11.00	10.24	11.70*	.....	8.93	11.00	9.15	10.85
5th week	.....	.....	.....	.....	8.50	11.46	8.08	11.46
6th week	.....	.....	.....	.....	9.42	12.26	9.20	12.14
Average of recovery period	9.27	11.40	10.36	12.24	9.32	12.36	9.77	12.07

* 4 days.

9. *Adrenal corticoids (by Dr. Konrad Dobriner):* During the first three weeks of immobilization in both subjects there was a definite although variable increase in urinary corticoids. Interpretation is complicated, however, by the considerable

10. *Other factors in the urine:* During the last four control weeks the average daily urinary output among the four subjects was 1,684 cc., during immobilization 1,919 cc. and 1,819 cc. during the first four recovery weeks. The daily fluid intake was not fixed

but the subjects were asked to take a minimum of 2,000 cc. The intake actually ranged between 2,000 and 2,400 cc. throughout all periods of study and averaged 2,069 cc. during control, 2,051 cc. during immobilization and 2,140 cc. during recovery.

TABLE IX

EFFECT OF IMMOBILIZATION UPON SERUM CALCIUM LEVELS

Subject	Control		Last Four Immobilization Weeks and First Two Recovery Weeks					Recovery	
	No. of Determinations	Range and Average of last 4 Wk., mg./100 cc.	No. of Determinations	Range and Average Value, mg./100 cc.	No. of Determinations higher than 11.5 mg./100 cc.	Maximal Serum Ca Value, mg./100 cc.	Week of Occurrence of Maximal Value	No. of Determinations	Range and Average of last 4 Wk., mg./100 cc.
E. M.	5	11.2 (11.0–11.4)	8	11.6 (10.9–12.0)	4	12.0	5th immobilization	2	11.1 (10.6–11.7)
C. O.	5	10.9 (10.5–11.6)	8	11.4 (9.5–12.7)	3	12.7	1st recovery	1	10.5
A. S	2	11.0 (10.7–11.2)	5	11.8 (11.1–12.3)	4	12.3	2nd recovery	2	10.9 (10.8–11.0)
S. W.	2	10.5 (10.2–10.8)	5	11.9 (10.7–12.6)	2	12.6	2nd recovery	2	10.9 (10.2–11.7)

There were no significant alterations in urinary specific gravity measured daily throughout the experiments.

11. *Blood chemistry studies:* There were no significant changes during the experiments in the blood levels of total proteins, phosphorus, sodium or potassium.

During the last three weeks of immobilization and first two recovery weeks two or more serum calcium levels in each of the four subjects were found to be higher than the generally accepted high normal value of 11.5 mg. per cent. (Table IX.) The maximum serum calcium levels in three of the subjects were 12.7 (C. O.), 12.3 (A. S.) and 12.6 (S. W.) mg. per cent; these maximum values were all found in the second recovery week. In A. S. and S. W., single values of 11.9 mg. per cent were found early in the control period. The maximum serum calcium value in E. M. was 12.0 mg. per cent and occurred in the fifth immobilization week.

B. Physiological Studies. 1. *Basal metabolism:* Tests of the basal metabolic rate performed at weekly intervals throughout the experiments showed a decline during immobilization, ranging from 1.0 to 4.3 calories per sq. m. per hour, averaging 2.4. This represents a reduction in basal heat production or oxygen consumption ranging from 3.1 to 11.5 per cent, averaging 6.9 per cent. In recovery, the basal metabolic rate returned to control levels within three to four weeks.

2. *Muscle strength:* Tests on the ergometer showed decreases in muscle strength during immobilization; these decreases were more marked in the immobilized leg muscles than in the other muscle groups tested.

Strength of the biceps muscle groups tested by the flexed arm pull showed an average decline among the four subjects of 6.6 per cent. Strength of the shoulder and arm muscles tested by the straight arm pull showed an average decline of 8.7 per cent. Decline in the strength of the anterior tibial muscle groups in the foot pull ranged from 7.8 to 20.6 per cent with an average decline of 13.3 per cent. Decline in the strength of the gastrocnemius-soleus muscle groups ranged from 11.8 to 31.0 per cent with an average decline of 20.8 per cent. In recovery, it required approximately four weeks for muscle strength to return to

control levels. Measurements of the strength of the grip and of abdominal and back muscles revealed no significant decreases at the end of the immobilization period.

3. *Girth of extremities:* In the first pair of subjects, measurements were made of the girth of the arms. The decrease in girth resulting from immobilization amounted to approximately 2 per cent for both upper arms and forearms.

Measurements of the girth of the thighs and calves were made in all four subjects, a more accurate measuring device being employed in the second pair. In the first pair of subjects, the decrease in the circumference of the thighs was 5.0 per cent for E. M. and 2.1 per cent for C. O. In the second pair of subjects the decrease in the circumference of the thighs was 3.6 per cent for A. S. and 4.8 per cent for S. W.

Decreases in the circumference of the calves were 5.5 and 6.0 per cent respectively in the first pair of subjects and 5.6 and 6.3 per cent in the second pair. When these decreases in the girth of the calves are transposed into decreases in the cross sectional area, a better conception of the extent of muscle atrophy is obtained; the decreases in the cross sectional area amounted to 4.2 to 10.0 per cent for the thighs and 9.7 to 12.5 per cent for the calves. If it is supposed that no appreciable volume decreases were occurring in any structure in the legs other than muscle, it is evident that an appreciable extent of muscle atrophy took place.

In the recovery period, five to six weeks was required for the legs to return to their original circumference.

4. *Tilt table:* Immobilization brought about a definite deterioration in the mechanisms essential for adequate circulation in the erect position. Within one week of the time immobilization was instituted, there began to develop an increasing tendency of the subjects to faint during tilt table tests.

Analysis of tilt table tests and correlation of data on pulse rate and blood pressure with the observed general reactions of the subject, indicated that the pulse pressure was the most important factor involved in the response of the circulation to tilting. With the subject standing in the upright position on the tilt table, it was found that when the pulse pressure became reduced to between 10 and 12 mm. of mercury a critical level was reached at which circulation became impaired, dizziness and pallor appeared and fainting followed shortly thereafter. The degree of change in pulse pressure also correlated closely with the subjects' reactions. Next in importance were fall in systolic pressure and degree of change in pulse rate. Graybiel and MacFarland,[41] in an analysis of tilt table tests on ninety-one normal individuals, concluded that pulse pressure and fall in systolic pressure were the most important factors denoting a failing circulation.

Figure 7 shows the percentage change from the resting levels of pulse rate and pulse pressure, resulting when the subjects were tilted to 65 degrees feet downward for twenty minutes. A normal, healthy individual accustomed to upright activity (as exemplified by our subjects during the control period), when tilted for twenty minutes will exhibit an increase in pulse rate and decrease in pulse pressure of 40 to 70 per cent from levels obtained in the resting horizontal position. The graph shows that during immobilization the changes in pulse rate and pulse pressure on tilting became more marked (generally greater than 70 per cent) and an increased frequency of fainting in tilt table tests developed. For one subject (S. W.), who fainted during nearly every test, the method of charting has been altered so that the minutes required to faint are plotted on the ordinate line. During immobilization this subject fainted at much shorter intervals of time.

Toward the end of the immobilization period all four subjects developed purpuric hemorrhages about the feet and ankles in the tilt table tests. These hemorrhages extended to the knees in one subject and to the mid-thigh in another. (Platelets were abundant in the blood smears throughout the

experiment. The prothrombin time was not altered significantly. The Rumpel-Leeds tourniquet test on the arm was normal. The average daily vitamin C intake was 144 mg.)

Some of the underlying factors in this circulatory deterioration during immobilization were explored. Experiments carried out on S. W., and shown in Figure 7, would seem to indicate that the legs are probably the principal vascular area in which important changes occur. At the end of the immobilization period when S. W. was fainting during tilt table tests consistently after six minutes, tilt table tests were performed on four successive days. On the first and third days, tests were performed with his legs wrapped firmly in Ace bandages from the feet to the groin; during these tests he was able to stand for more than twenty minutes without fainting. On the second and fourth days, tests were done in the usual fashion without bandages;

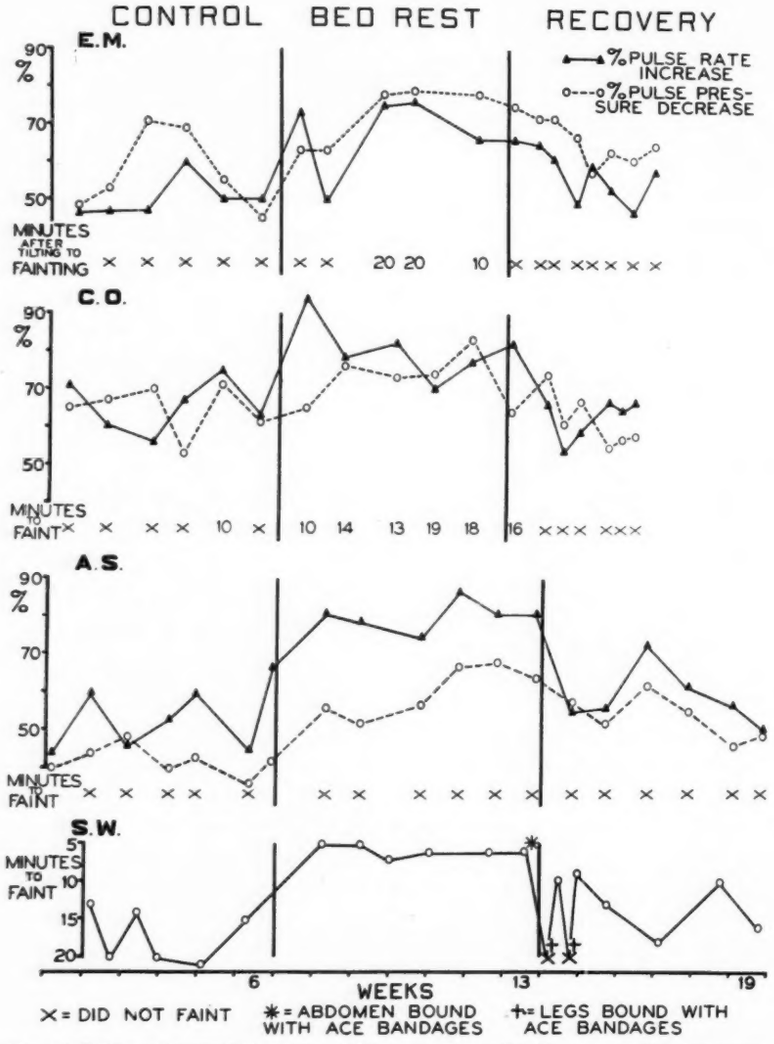

FIG. 7. Effect of immobilization on the responses of pulse rate and pulse pressure to tilting to 65 degrees feet downward for twenty minutes in four normal male subjects. The chart also shows for each test the number of minutes in the tilted position required for fainting to occur; an "x" indicates that on that test the subject remained in the tilted position for more than twenty minutes without fainting. For subject S. W., who fainted on nearly every test, the method of charting has been altered so that minutes required for fainting to occur are plotted on the ordinate line.

during these tests he fainted in ten and nine minutes. Wrapping the abdomen tightly in Ace bandages had no effect upon the subject's reaction to tilting; during this test S. W. fainted in six minutes.

Measurements of the circumference of the legs during tilt table tests were carried out on the second pair of subjects. Measurements were made in the horizontal position, immediately after assuming the tilted position, at the end of the period of tilting and immediately after resumption of the horizontal position. Differences in these four observations were used to calculate changes in circumference due to (a) venous engorgement and (b) increases in extravascular fluid. In subject A. S., who stood for twenty minutes in all tilt table tests, comparison of the values obtained in control period tests with those of immobilization period tests suggested that during bed rest there was a greater increase in extravascular fluid and a greater progressive increase in venous engorgement than occurred in tests during the control period. In S. W., who fainted much more rapidly on tests during immobilization, a greater increase in extravascular fluid took place during immobilization *within five minutes* of tilting than occurred in thirteen to twenty minutes of tilting in control period tests.

Recovery from the type of circulatory deterioration demonstrated by tilt table tests took place approximately three to four weeks after the subjects became ambulant.

5. *Blood volume:* The decline in plasma volume in the four subjects at the end of three weeks of immobilization ranged from 120 to 320 cc., averaging 191 cc. or 6.3 per cent. Decreases in total blood volume ranged from 180 to 366 cc., with an average decrease of 275 cc. or 5.4 per cent. During the remaining three to four weeks of the immobilization period the blood volume tended to return toward control levels; there was an average increase of 121 cc. in plasma volume and 111 cc. in total blood volume by the end of immobilization. In the recovery period, the plasma and total blood volumes returned to control levels within three to four weeks.

6. *Circulation time:* Measurements of the speed of the circulation from arm to tongue, arm to perineum and arm to feet by the decholin and macasol methods showed no changes during the immobilization period.

7. *Blood coagulation studies:* Coagulation times by the Lee-White method done on blood from arm veins showed no significant changes as a result of immobilization; indeed, coagulation times tended to be slightly longer during the bed rest period. Prothrombin time determinations, performed on the second pair of subjects, showed a slight prolongation of questionable significance during immobilization.

8. *Exercise tolerance tests:* Master tests, performed in the control period and again in recovery as soon as the subjects were ambulant, showed marked decreases in exercise tolerance as a result of immobilization. Increases in pulse rate and systolic blood pressure after exercise were considerably greater following immobilization. In general, from three to six minutes were required for the pulse and from five to seven minutes for the systolic pressure to return to pre-exercise levels; whereas in control period tests using the same number of climbs, two minutes or less was usually required for the pulse and four minutes or less for the systolic pressure to return to pre-exercise levels.

Schneider tests showed significant declines in scores in all four subjects following immobilization. The average of pre-immobilization scores was +9 points, the average following immobilization was +3. The range of decline in scores was 4 to 9 points, averaging 6 points. Four to six weeks of recovery were required for the Master and Schneider tests to return to control period levels.

9. *Heart size:* X-rays of the chest by standard chest technic, taken every three weeks throughout the studies, showed considerable variation in the apparent size of the heart and no evident tendency toward

reduction in the size of the heart during the immobilization phase.

10. *Electrocardiograms:* There were minor changes during immobilization in electrocardiograms taken with the subjects in the usual resting, horizontal position. The rate was slightly increased and there were minor reductions (1.0 to 1.5 mm.) in the amplitude of the T waves in the second and third leads. No other significant changes were noted which could not be attributed to the slight increase in rate.

Electrocardiograms were made in conjunction with tilt table tests in the second pair of subjects. Records made while the subject was being tilted showed the following changes during the immobilization period: increase in rate in both subjects; slight reduction in the height of R_1 and T_1 and deepening of S_1 in one subject (A. S.) and reduction in height of T_2 in the other subject (S. W.). These changes in the form of the electrocardiogram disappeared during the recovery period.

11. *Resting pulse rate and blood pressure:* During immobilization there was an average increase among the four subjects in resting pulse rate of 3.8 beats per minute, ranging from 1.6 in one subject to 8.3 in another. During the first three weeks of recovery there was an additional average increase of 4.7 beats per minute. From the third recovery week the resting pulse rate declined toward the control level. In the first pair of subjects (recovery period four weeks), the resting pulse rate had not returned to the control level at the end of the fourth week; in the second pair of subjects, the rate had almost returned to the control level at the end of the sixth week. There were no significant changes in the resting arterial blood pressures. It has been supposed that the blood pressure fell during long periods of bed rest; actually, in this experiment systolic blood pressures during immobilization averaged 2.0 mm. higher than the control period resting systolic pressures.

12. *Hematocrits and "blood counts":* No significant changes attributable to bed rest occurred in hematocrits or in white cell counts, red cell counts or hemoglobin determinations. In the first pair of subjects, blood volume determinations were performed every two weeks and blood was drawn for chemistry at weekly intervals; the estimated average weekly blood loss was 70 cc. This may have contributed to a gradual fall in hematocrit in this pair of subjects throughout the entire four and one-half months of the experiment of 3 volumes per cent in one subject and 4 volumes per cent in the other. In the second pair of subjects on whom blood chemistry and blood volume determinations were done less frequently, there was a gradual fall in hematocrit of 1 and 2 volumes per cent respectively.

TABLE X
CHANGES IN BODY WEIGHT

Subject	Control	Immobilization		Recovery	
	Weight Change (last 4 wk.), Kg.	No. of Wk.	Weight Change, Kg.	No. of Wk.	Weight Change, Kg.
E. M.	−0.9	6	−1.2	4	+1.3
C. O.	+0.4	6	+1.6	3	+0.8
A. S.	−0.4	7	+1.0	6	+1.9
S. W.	−0.9	7	−0.7	6	+1.1

13. *Respiration studies:* There were no significant changes during immobilization in determinations of vital capacity (subject horizontal), ventilation at rest, maximum ventilation capacity, breath holding and the Flack test. It is of interest that although maximum ventilation capacity was unimpaired during immobilization, more subjective effort seemed to be required to achieve the same result as was obtained during the control period. The subjects became red-faced and definitely fatigued after performing the test during the latter part of the immobilization period.

14. *Body weight:* The body weight changes during the various periods of study are given in Table x. The changes were small during

each period. During immobilization two subjects gained weight and two subjects lost weight. All four subjects gained weight in recovery.

15. *X-rays of the skeleton:* X-rays were taken of the spine and long bones at three-week intervals on the first pair of subjects. No detectable change in bone density took place during the experiment.

PSYCHOBIOLOGIC EFFECTS OF IMMOBILIZATION*

The four subjects of this experiment, none of whom had a major psychiatric disorder, were studied to determine the psychobiologic effects of immobilization. Data was collected from psychologic examinations, psychiatric interviews and recordings of the subjects' daily experiences. The list contained sixty-five items relating to physical and mental activity and energy, psychosomatic reactions, mood changes, sleep and sexual activity and reactions to doctors, nurses and visitors.

The data revealed that the reactions to immobilization were markedly variable from subject to subject, both in pattern and degree, and were predominantly expressions of the subjects' dominant personality factors.

A subject's immediate reaction to immobilization was similar to that which he experienced in other situations of stress and danger, each subject according to his own dominant personality traits. Thus, one subject whose personality was marked by feelings of insecurity reacted with predominant anxiety and dependency; another who was aggressive became hostile; a Nisei who had been trained to suppress all outward signs of emotion became placid. These reactions occurred during the two days when the cast was fitted, again during the first forty-eight hours of immobilization and once more during the first few days after the cast had been removed. They therefore appeared to be reactions to new and potentially dangerous situations.

During the course of the six to seven weeks of immobilization each subject manifested, either overtly or indirectly, signs of anxiety, hostility, increased sexual tension and discomfort. Changes also took place during immobilization in mental activity, physical activity and the sleep pattern. The intensity of all these reactions and changes in behavior varied with the personality of the subject. Anxiety, hostility and sexual tension reached their individual maximums at varying periods in each subject. Complaints of physical discomfort (impaired sleep, stiffness and soreness of muscles) were frequent during the first one to two weeks. Thereafter, the subjects were relatively comfortable and carried on activity, including reading and writing with moderate ease. It is to be noted that the Nisei, in keeping with his personality, made almost no complaints of discomfort. Sleep was improved over what it had been in the control period in the subject who reacted with dependency, was unchanged or slightly impaired in others.

Among the physiologic changes observed, all four subjects had a slight decrease in appetite and a gradually increasing generalized weakness with ease of fatigue on the slightest exertion (such as using the bedpan) In two subjects, there was a very slight tendency toward constipation; the other two subjects, who by personality were accustomed to setting patterns of behavior for themselves, set a routine of using the bedpan every evening. In recovery, the subjects noted mild dizziness for one to two days and unsteadiness of the legs for six to eight days. Stiffness and even soreness of the joints, particularly the knees, which began mildly during the last two to three weeks of immobilization, was evident for three to six weeks in recovery. One subject, who had had an injury to one knee years previously, had soreness of both knees for three to four months.

The inconveniences of the experimental procedure, with the exception of immo-

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bilization in the cast, were accepted by all subjects with great equanimity; however, any disturbance of the good interpersonal relationship of the subject with the doctors or nurses immediately resulted in a violent reaction similar to what the subject experienced in a situation of stress or danger.

COMMENTS

The data presented in this study now make it possible to evaluate the potential contribution of immobilization *per se* to the variety of metabolic and physiologic changes which have been observed to be associated with trauma and disease states in man.

There have been several reports in the literature describing nitrogen and calcium losses following infectious diseases,[57,58] fractures and surgical procedures[58–63] and in metabolic disorders.[64,65] The possibility that disuse atrophy from immobilization *per se* might contribute in any significant degree to these metabolic disturbances has been minimized or overlooked. The conditions under which these patients were carried out did not permit a quantitative evaluation of the effects of disuse atrophy since they were limited to patients with traumatic or infectious disorders.

A comparison of the data obtained in this study with those provided by a study on patients with a fracture permits such an evaluation. The best comparative data are provided by the studies of Howard[66] since the extent and duration of immobilization was most nearly comparable to the conditions of our experiment. This investigator observed total nitrogen losses following a fracture ranging from 124 to 257 Gm., with an average loss of 190 Gm., during four to five weeks after the fracture in five otherwise healthy, young males. The total nitrogen losses of our four subjects over a similar period of immobilization were, on the average, one-fourth to one-fifth as great. It is evident that immobilization of a healthy person provides a stimulus to increased nitrogen metabolism of an appreciable magnitude. Further comparison of Howard's patients with our subjects revealed differences in the tempo at which the increase in nitrogen metabolism occurred. Thus, following fracture the increase in nitrogen excretion occurred more rapidly than in the immobilized, healthy adult. After fracture the nitrogen losses were evident within forty-eight hours and reached maximum values by the sixth day. In the healthy, immobilized subject, no increase in nitrogen excretion was evident before the fifth day and the maximum was not reached until the tenth day. It would appear that immobilization does not contribute to the early outpouring of nitrogen following trauma or operative procedures and has no disadvantageous effects on nitrogen metabolism until after the first five or six days.

As in the fracture cases studied by Howard, there were considerable differences in the nitrogen losses between the individual subjects. The nitrogen losses ranged from 30 to 84 Gm. These variations could not be correlated with differences in body type nor could they be related to differences in the state of nutrition of the subjects since all were in an excellent state of well being and nutrition. We were therefore dealing with different responses of the individual subject of quite another character than the variations described by Munro and Cuthbertson[67] for rats in which the nitrogen losses after trauma could be regularly related to the previous state of nutrition; rats debilitated by a protein-free diet failed to exhibit the rise in nitrogen excretion following fracture which was regularly observed in rats on an adequate protein intake.

In view of the current trend of thought which would relate the nitrogen disturbances after disease states and trauma to alterations in the quality and quantity of the adrenal cortical steroidal hormones,[68] it is of interest that in only one of the subjects was there any correlation between nitrogen excretion and the urinary content of 17-ketosteroids. In two subjects in whom urinary glycogenic corticoid excretion was determined as well, no significant differences were observed between the control

and immobilization periods. These subjects exhibited neither the increase in urinary corticoids nor the decrease in 17-ketosteroid excretion required by this concept, with one exception. Subject E. M., who exhibited the maximal loss of nitrogen during immobilization, showed a decrease in 17-ketosteroid excretion from the control values of 11.1 mg. per twenty-four hours to an average value of 8.5 mg. per twenty-four hours during the period of immobilization.

The nitrogen losses may now be considered in relation to concomitant changes in phosphorus, potassium and sulfur metabolism. There was remarkably good agreement from week to week in the ratio between urinary sulfur and nitrogen excretion. The ratio of nitrogen to sulfur was consistently that in which these substances are present in muscle protoplasm. The correlation between nitrogen and phosphorus excretion was less good. In three of the subjects, nitrogen excretion during immobilization was significantly greater than was anticipated from the phosphorus excretion not accounted for by calcium, assuming a ratio of nitrogen to phosphorus of 14.7 to 1. In the fourth subject, a discrepancy of about 30 per cent existed in the opposite direction, i.e., less nitrogen was excreted than expected from the concomitant excretion of phosphorus. There was a poor correlation between nitrogen and potassium metabolism. There was a tendency for potassium to move in the same direction as nitrogen and for the potassium balances to become negative during the period of immobilization; however, the quantitative relationships were not close, and there were wide week to week fluctuations in the potassium excretion. In each of the four subjects, the theoretical nitrogen losses based on potassium excretion exceeded the measured nitrogen losses by 61, 46, 27 and 50 per cent, respectively.

Other metabolic studies have yielded equally divergent results with respect to the relation of nitrogen to phosphorus and potassium metabolism. In Benedict's study of a fasting man,[69] after an initial diuresis of potassium and phosphorus, the potassium, phosphorus, sulfur and nitrogen losses occurred in the ratio in which these elements exist in muscle protoplasm. On the other hand, Howard's fracture patients stored potassium while they were losing nitrogen and sulfur.[66]

It is doubtful whether the data relating to nitrogen, phosphorus and sulfur metabolism during immobilization can contribute anything of value to a discussion of the controversial subject of "deposit" protein[70] versus structural or protoplasmic protein as the source of the nitrogen lost. The studies of Schoenheimer and his associates, which have shown the presence of a dynamic equilibrium between the body proteins, tend to throw doubt on the existence of separate categories of proteins in the living organism. It is of interest that the nitrogen losses of well nourished individuals who had been receiving a more than adequate protein diet were at all times accompanied by losses of sulfur in the approximate ratio in which these elements exist in protoplasm. Were there a separate compartment of labile deposit protein in these subjects, it should be of considerable magnitude in view of their previous diet and should have been readily drawn upon during the period of nitrogen loss. Such a phenomenon would have manifested itself in a significant increase in the nitrogen-sulfur ratio during the immobilization phase. Actually, such increases in the nitrogen-sulfur ratio as were observed during the immobilization period over that of the control were extremely small, of short duration and undoubtedly not significant.

It is unfortunately not possible to make a strict comparison of the total calcium losses of our subjects during immobilization with that exhibited by the group of fracture patients studied by Howard, inasmuch as the calcium intake of the latter group was not kept constant during the period of study. With these reservations in mind, the statement seems reasonably justified that over a corresponding period of time the average total excretion of calcium by the healthy,

immobilized adults was at least one-half that of the fracture group. As with the nitrogen excretion, there was a wide variation between subjects as to the extent of calcium excretion during immobilization, two excreting calcium in amounts equal to those found in fractures. Only a very questionable correlation could be made between calcium excretion and body type, the greatest losses occurring in the two tall and slender subjects.

X-rays of the skeleton failed to show evidence of osteoporosis. This might be anticipated from the magnitude of the calcium loss which was equivalent to 1 to 2 per cent of the total calcium content of the skeleton. It is estimated that at least 10 per cent of the total skeletal calcium must be lost for x-rays to show evidence of decalcification.

The alterations in urinary calcium excretion of immobilized healthy subjects and fracture patients are more strictly comparable since the urinary excretion of calcium is not usually greatly altered by minor alterations in calcium intake. The maximum urinary calcium excretion range of seventeen patients with fracture or osteotomy reported by Howard[55] was 295 to 670 mg. per day with an average maximum of 510. The average maximum daily urinary excretion of the immobilized group was approximately two-thirds that of the fracture group.

These significant increases in urinary calcium excretion, which were far greater than the increases observed in fecal calcium, are of interest in relation to the problem of urinary tract stone formation. Stone formation of the calcium phosphate variety often presents a major complication during immobilization, particularly of orthopedic patients. Major J. J. Joelson[71] reported that the incidence of nephrolithiasis at Crile General Hospital was 7 per cent in cases of fractured femur and 2 per cent in all orthopedic patients. Flocks[72] has given the incidence as ranging from 5 to 15 per cent in orthopedic patients requiring extensive immobilization. Others have reported unofficially incidences as high as 25 per cent in patients with spinal cord injury.

All of the changes observed during immobilization in the urinary constituents concerned with calcium phosphate solubility would favor the precipitation of calculi, except for the very slight rise in urinary volume. There was a definite and sustained rise of urinary pH throughout the immobilization period which is unfavorable for calcium phosphate solubility. The rises in urinary calcium and phosphate provided an additional tax on the urine to retain these electrolytes in solution. In the normal individual, a shift in urine toward the alkaline side and an increase in urinary calcium excretion is regularly accompanied by an increase in urinary citric acid.[56] This latter metabolite, by virtue of its capacity to form a poorly ionized, very soluble calcium-citrate complex, exercises a favorable effect on calcium solubility. The absence of any increase in urinary citric acid during immobilization in the face of a higher pH and a greater content of calcium and phosphorus, deprives the organism of this protective device and favors calcium phosphate precipitation. There is no explanation at present for the failure of urinary citric acid to rise during the hypercalcinuria and increased pH during immobilization.

It is unlikely that this derangement is of clinical significance for short periods of immobilization since, although urinary calcium excretion began to increase promptly after the institution of immobilization, high levels were not reached prior to the third or fourth weeks. The possibility of urinary calculi formation would thus appear to be a hazard only to those patients immobilized for longer periods. Renal colic and hematuria have seldom occurred during recumbency in less than ten weeks.[73] However, in the tropics, where urine volumes may become markedly reduced, large amounts of calcium phosphate sand and crystals were found within three to four weeks of immobilization in soldiers in North Africa with fractures and severe flesh wounds.[74]

The alterations in calcium excretion during immobilization were accompanied by slight rises in the level of the serum calcium which ranged from 0.8 to 2.1 mg. per cent. In every instance, the original levels were resumed during the last four weeks of the recovery period although in three instances the maximum values occurred during the first two weeks of the recovery period at which time calcium excretion had just begun to diminish. Alkaline phosphatase blood levels were not obtained. Howard[55] reported a rise in alkaline phosphatase in only one of seventeen patients in his series; this was in a patient with a fracture caused by a bullet.

The progressive reduction in creatine tolerance during immobilization is attributable to the progressive development of a functional impairment of the capacity to store creatine which involved a fairly considerable mass of muscle. The explanation for the absence of significant changes in creatinuria on those days in which no creatine tolerance tests were carried out would appear to reside in the fact that the creatine in the diet did not exceed the capacity of the normal muscle mass in the unimmobilized portions of the body to retain the creatine. This is an explanation which is consistent with many observations which have shown that in patients with localized muscle defects, such as those which result from poliomyelitis, the presence or absence of creatinuria is dependent upon the proportion of damaged to undamaged muscle. However, the extra load imposed by the ingestion of 1.32 Gm. of creatine given on the test day exceeded the capacity of the muscle mass during the immobilization phase and served to unmask the muscle impairment of the immobilized areas. The validity of the creatine tolerance test as a measure of functional or pathologic muscle damage has been well established for Graves' disease, poliomyelitis and progressive muscular dystrophy. In the present study, it would indicate that a functional impairment in muscle creatine metabolism occurred during immobilization and was reversed when the subjects were restored to full activity. This impairment in creatine metabolism was accompanied by a significant decrease in muscle mass and muscle strength in the immobilized limbs. The effect of immobilization on creatine tolerance observed in the present study would not appear to modify the interpretation of the test in Graves' disease which does not involve the complete immobilization to which those in our study were subjected.

The altered response of the circulation to the upright position as manifested by dizziness, unsteadiness and the tendency to faint has been experienced by many after even brief illnesses requiring bed rest. The results of the tilt table tests in this experiment indicate that bed rest is at least partially responsible for this type of circulatory deterioration and that evidences of it may be detected within one week of the assumption of the recumbent position.

The experiments in which fainting on the tilt table during immobilization was prevented by wrapping the legs in Ace bandages and was not prevented by wrapping the abdomen, point to the legs as the principal vascular area in which important changes occur.

Some of the factors involved in the mechanism of gravity shock and the attempts at preservation of circulation in the upright position are peripheral arterial vasoconstriction, capillary permeability, venous tone, muscle tonus or intramuscular pressure as well as the total circulating blood volume. Investigation of some of these factors and their possible alteration during bed rest was attempted.

One of the methods employed was measurement of leg circumference during tilting. Small and rapid changes in the size of the legs could be readily detected by the use of the device we have described. Analysis of the changes in leg circumference during and following tilting suggested that during the immobilization phase (as compared with the control period), there occurred both greater increases in extravascular fluid and greater progressive increases in venous en-

gorgement in the tilted position. These changes imply either impaired venous or leg muscle "tone" during immobilization or the participation of both factors. Intramuscular pressures were not measured. However, the observed leg muscle atrophy may be relevant and it may have been responsible for lowered muscle tone and reduced support for the leg veins.

The occurrence of purpuric hemorrhages about the feet and ankles in tilt table tests during immobilization is evidence of increased capillary wall fragility or permeability.

The changes in circulating blood volume brought about by immobilization were small and barely significant. Taylor, Erickson, Henschel and Keys[12] have reported more marked changes in three weeks of bed rest in which their subjects were not immobilized and their dietary intake was reduced; they found an average plasma volume loss of 15.5 per cent and total blood volume loss of 9.3 per cent, approximately twice the change found in our subjects.

Relative to the problem of phlebothrombosis, studies of blood coagulation (Lee-White coagulation time and prothrombin time) carried out on arm vein blood showed no increased tendency to coagulation as a result of immobilization. Indeed, Lee-White coagulation times tended to be slightly longer during the bed rest period. These findings suggest that in young, immobilized individuals, in the absence of disease, anesthesia or analgesics, there is no increased tendency of the blood of the general circulation to undergo coagulation.

It was found that there was an average decline in basal metabolism of 6.9 per cent during the immobilization period. It may be safely assumed that the total energy metabolism of the subjects also declined to an even greater extent. From these considerations alone all subjects might have been expected to gain weight since the dietary intake was constant. On the other hand, there were parallel losses of nitrogen of considerable magnitude equivalent to calculated losses of muscle protoplasm ranging from 0.95 to 2.67 Kg.

The actual weight changes were small. (Table x.) Two subjects gained and two lost weight during immobilization. C. O. gained 1.6 Kg. (his theoretical muscle protoplasm loss was 0.95 Kg.) and A. S. gained 1.0 Kg. (his theoretical muscle protoplasm loss was 1.44 Kg.). E. M. and S. W., who lost greater amounts of nitrogen (theoretical muscle protoplasm losses, 2.67 Kg. for E. M. and 1.79 Kg. for S. W.), lost 1.2 and 0.7 Kg. in weight, respectively.

These relatively small changes in weight are probably the result of the simultaneous loss of muscle protoplasm and storage of fat or carbohydrate. In three of the four subjects, definite development of fat folds in the abdominal wall was apparent at the end of the immobilization period. Measurements of changes in total body water were not carried out but during immobilization there was no storage of sodium or potassium such as would suggest retention of water.

Although we have demonstrated certain detrimental effects of immobilization, particularly in mineral metabolism and circulation, the effect upon basal metabolism gives support to the opinion that bed rest is beneficial in the treatment of tuberculosis. One of the principal reasons for the advocacy of bed rest therapy in this disease has been the inference that energy production is reduced during bed rest. The 6.9 per cent average decline in basal metabolism during immobilization in this experiment would indicate that there is a small but definite reduction in basal energy production during complete bed rest as well as a lowering of total energy production resulting from decreased activity.

The long period required for the various metabolic and physiologic functions to become stabilized following immobilization was impressive. The recovery of metabolic functions in particular was sluggish. (Tables XI, XII, XIII and XIV.) There was a pronounced retention of nitrogen and phosphorus during recovery which continued for six weeks. Calcium metabolism appeared

TABLE XI

METABOLIC BALANCES, SUBJECT E. M., SEVEN-DAY PERIODS—ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen						Calcium						Phosphorus						Potassium					
	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake*	Output			Balance*	Variation from Control Base-line
		Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total		
Control																								
III	13.55	11.23	1.01	12.24	+1.31	−0.03	0.856	0.078	0.690	0.768	+0.088	−0.043	1.460	0.820	0.517	1.337	+0.123	−0.205	3.15	2.63	0.374	3.00	+0.15	+0.14
IV	13.55	11.63	0.89	12.52	+1.03	−0.31	0.863	0.094	0.697	0.791	+0.072	−0.059	1.485	0.823	0.517	1.340	+0.145	−0.183	3.15	2.56	0.334	2.89	+0.26	+0.25
V	13.60	11.25	0.88	12.13	+1.47	+0.11	0.849	0.068	0.660	0.728	+0.121	−0.010	1.499	0.781	0.516	1.297	+0.202	−0.126	3.15	2.98	0.377	3.36	−0.21	−0.22
VI	13.59	11.12	0.83	11.95	+1.64	+0.28	0.855	0.069	0.690	0.759	+0.096	−0.035	1.473	0.741	0.497	1.238	+0.235	−0.093	3.15	2.68	0.356	3.04	+0.11	+0.10
VII	13.54	11.11	0.83	11.94	+1.60	+0.24	0.852	0.048	0.650	0.698	+0.154	+0.023	1.506	0.840	0.344	1.184	+0.322	−0.006	3.15	2.69	0.330	3.02	+0.13	+0.12
VIII	13.59	11.36	1.03	12.39	+1.20	−0.16	0.849	0.048	0.793	0.841	+0.008	−0.123	1.499	0.736	0.426	1.162	+0.337	+0.009	3.15	2.96	0.426	3.39	−0.24	−0.25
IX	13.55	11.79	0.76	12.55	+1.00	−0.36	0.853	0.036	0.552	0.586	+0.267	+0.136	1.490	0.774	0.300	1.074	+0.416	+0.088	3.15	2.86	0.260	3.12	+0.03	+0.02
Control Base-line, Average of Last Four Weeks	13.57	11.35	0.86	12.21	+1.36	0.0	0.852	0.050	0.671	0.721	+0.131	0.0	1.492	0.773	0.391	1.164	+0.328	0.0	3.15	2.80	0.343	3.14	+0.01	0.0
Immobilization																								
X	13.55	13.51	0.89	14.40	−0.85	−2.21	0.853	0.085	0.674	0.759	+0.094	−0.037	1.490	0.941	0.464	1.405	+0.085	−0.243	3.15	3.08	0.360	3.44	−0.29	−0.30
XI	13.55	14.62	1.12	15.74	−2.19	−3.55	0.856	0.087	0.817	0.904	−0.048	−0.179	1.491	0.962	0.574	1.536	−0.045	−0.373	3.15	3.12	0.390	3.51	−0.36	−0.37
XII	13.56	13.86	0.91	14.77	−1.21	−2.57	0.852	0.102	0.733	0.835	+0.017	−0.114	1.507	0.915	0.517	1.432	+0.075	−0.253	3.15	3.00	0.333	3.33	−0.18	−0.19
XIII	13.55	12.44	1.01	13.45	+0.10	−1.26	0.852	0.119	0.776	0.895	−0.043	−0.174	1.507	0.850	0.529	1.379	+0.128	−0.200	3.15	3.15	0.343	3.49	−0.34	−0.35
XIV	13.55	12.37	1.10	13.47	+0.08	−1.28	0.853	0.106	0.896	1.002	−0.149	−0.280	1.490	0.859	0.622	1.481	+0.009	−0.319	3.15	3.15	0.326	3.48	−0.33	−0.34
XV	13.55	12.32	0.95	13.27	+0.28	−1.08	0.851	0.110	0.780	0.890	−0.039	−0.170	1.524	0.891	0.537	1.428	+0.096	−0.232	3.15	3.30	0.323	3.62	−0.47	−0.48
Average of Immobilization	13.55	13.19	0.99	14.18	−0.63	−1.99	0.853	0.102	0.779	0.881	−0.028	−0.159	1.501	0.903	0.540	1.443	+0.058	−0.270	3.15	3.13	0.346	3.48	−0.33	−0.34
Recovery																								
XVI	13.55	12.04	0.90	12.94	+0.61	−0.75	0.854	0.087	0.743	0.830	+0.024	−0.107	1.514	0.854	0.526	1.380	+0.134	−0.194	3.15	2.86	0.290	3.15	0.00	−0.01
XVII	13.55	10.49	0.97	11.46	+2.09	+0.73	0.852	0.064	0.790	0.854	−0.002	−0.133	1.506	0.692	0.526	1.218	+0.288	−0.040	3.15	2.50	0.323	2.82	+0.33	+0.32
XVIII	13.55	9.96	0.99	10.95	+2.60	+1.24	0.852	0.060	0.746	0.806	+0.046	−0.085	1.506	0.694	0.462	1.156	+0.350	+0.022	3.15	2.57	0.290	2.86	+0.29	+0.28
XIX	13.55	9.07	1.17	10.24	+3.31	+1.95	0.852	0.043	0.747	0.790	+0.062	−0.069	1.506	0.667	0.503	1.170	+0.336	+0.008	3.15	2.85	0.390	3.24	−0.09	−0.10

* Potassium intake and balance figures corrected for additional intake from coffee of approximately 0.25 Gm. daily; these figures are probably accurate within ±0.10 Gm.

TABLE XII

METABOLIC BALANCES, SUBJECT C. O., SEVEN-DAY PERIODS—ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen						Calcium						Phosphorus						Potassium					
	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake*	Output			Balance*	Variation from Control Base-line
		Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total		
Control																								
III	13.80	11.00	1.13	12.13	+1.67	+0.13	0.869	0.109	0.680	0.789	+0.080	−0.050	1.540	0.879	0.409	1.288	+0.252	−0.026	3.76	3.28	0.216	3.50	+0.26	+0.28
IV	14.42	11.72	1.20	12.92	+1.50	−0.04	0.919	0.109	0.647	0.756	+0.163	+0.033	1.642	0.948	0.397	1.345	+0.297	+0.019	3.76	3.93	0.204	4.13	−0.37	−0.35
V	14.42	11.20	1.46	12.66	+1.76	+0.22	0.920	0.105	0.733	0.838	+0.082	−0.048	1.607	0.920	0.451	1.371	+0.236	−0.042	3.76	3.54	0.247	3.79	−0.03	−0.01
VI	14.42	11.57	1.25	12.82	+1.60	+0.06	0.920	0.126	0.714	0.840	+0.080	−0.050	1.623	0.939	0.422	1.361	+0.262	−0.016	3.76	3.58	0.195	3.78	−0.02	0.0
VII	14.42	11.68	1.10	12.78	+1.64	+0.10	0.920	0.098	0.583	0.681	+0.239	+0.109	1.623	0.927	0.357	1.284	+0.339	+0.061	3.76	3.63	0.159	3.79	−0.03	−0.01
VIII	14.40	11.92	1.31	13.23	+1.17	−0.37	0.920	0.134	0.667	0.801	+0.119	−0.011	1.637	0.946	0.417	1.363	+0.274	−0.004	3.76	3.54	0.204	3.74	+0.02	+0.04
Control Base-line, Average of Last Four Weeks	14.42	11.59	1.28	12.87	+1.54	0.0	0.920	0.116	0.674	0.790	+0.130	0.0	1.623	0.933	0.412	1.345	+0.278	0.0	3.76	3.57	0.201	3.78	−0.02	0.0
Immobilization																								
IX	14.40	12.42	1.29	13.71	+0.69	−0.85	0.919	0.200	0.754	0.954	−0.035	−0.165	1.642	1.006	0.440	1.446	+0.196	−0.082	3.76	3.45	0.214	3.66	+0.10	+0.12
X	14.42	12.29	1.21	13.50	+0.92	−0.62	0.921	0.254	0.707	0.961	−0.040	−0.170	1.621	1.024	0.429	1.453	+0.168	−0.110	3.76	3.60	0.216	3.82	−0.06	−0.04
XI	14.42	12.57	1.22	13.79	+0.63	−0.91	0.919	0.283	0.704	0.987	−0.068	−0.198	1.656	1.095	0.431	1.526	+0.130	−0.148	3.76	3.92	0.166	4.09	−0.33	−0.31
XII	14.42	11.97	1.25	13.22	+1.20	−0.34	0.920	0.314	0.804	1.118	−0.198	−0.328	1.637	1.070	0.477	1.547	+0.090	−0.188	3.76	3.78	0.166	3.95	−0.19	−0.17
XIII	14.42	12.38	1.18	13.56	+0.86	−0.68	0.920	0.319	0.800	1.119	−0.199	−0.329	1.639	1.025	0.462	1.487	+0.152	−0.126	3.76	3.76	0.146	3.91	−0.15	−0.13
XIV	14.42	12.47	1.26	13.73	+0.69	−0.85	0.920	0.335	0.754	1.089	−0.169	−0.299	1.639	1.063	0.444	1.507	+0.132	−0.146	3.76	3.62	0.200	3.82	−0.06	−0.04
Average of Immobilization	14.42	12.35	1.24	13.59	+0.83	−0.71	0.920	0.284	0.754	1.038	−0.118	−0.248	1.639	1.047	0.447	1.494	+0.145	−0.133	3.76	3.69	0.185	3.88	−0.12	−0.10
Recovery																								
XV	14.42	12.33	1.18	13.51	+0.91	−0.63	0.920	0.279	0.632	0.911	+0.009	−0.121	1.637	1.057	0.409	1.466	+0.171	−0.107	3.76	3.65	0.164	3.81	−0.05	−0.03
XVI	14.42	10.38	1.58	11.96	+2.46	+0.92	0.920	0.170	0.688	0.858	+0.062	−0.068	1.639	0.917	0.454	1.371	+0.268	−0.010	3.76	3.54	0.264	3.80	−0.04	−0.02
XVII	14.42	9.45	1.80	11.25	+3.17	+1.63	0.920	0.105	0.787	0.892	+0.028	−0.102	1.639	0.872	0.463	1.335	+0.304	+0.026	3.76	3.21	0.282	3.49	+0.27	+0.29

* Potassium intake and balance figures adjusted for additional intake from coffee of approximately 0.25 Gm. daily; these figures are probably accurate within ±0.10 Gm.

TABLE XIII

METABOLIC BALANCES, SUBJECT A. S., SEVEN-DAY PERIODS—ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen						Calcium						Phosphorus						Potassium						Sodium					
	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake*	Output			Balance*	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line
		Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total		
Control																														
I	14.42	11.83	2.03	13.86	+0.56	−0.62	0.920	0.108	0.622	0.730	+0.190	+0.028	1.639	0.961	0.466	1.427	+0.212	−0.033	3.76	3.32	0.520	3.84	+0.08	−0.30	4.00	3.00	0.200	3.20	+0.80	+0.34
II	14.42	11.72	2.03	13.75	+0.67	−0.51	0.920	0.136	0.703	0.839	+0.081	−0.081	1.639	0.985	0.457	1.442	+0.197	−0.048	3.76	3.00	0.523	3.52	+0.24	+0.02	4.00	3.50	0.230	3.73	+0.27	−0.19
III†	..	12.14	..	..	..	..	..	0.127	..	..	..	..	..	1.030	..	..	..	..	..	3.10	..	..	..	..	..	3.05				
IV	14.42	12.31	1.82	14.13	+0.29	−0.89	0.920	0.130	0.625	0.755	+0.165	+0.003	1.648	0.964	0.447	1.411	+0.237	−0.008	3.76	2.70	0.510	3.21	+0.55	+0.33	4.00	3.30	0.260	3.56	+0.44	−0.02
V	14.42	10.73	1.82	12.55	+1.87	+0.69	0.920	0.112	0.664	0.776	+0.144	−0.018	1.623	0.920	0.480	1.400	+0.223	−0.022	3.76	2.97	0.560	3.53	+0.23	+0.01	4.00	3.34	0.203	3.54	+0.46	0.00
VI	14.42	11.32	1.72	13.04	+1.38	+0.20	0.919	0.127	0.614	0.741	+0.178	+0.016	1.656	0.976	0.404	1.380	+0.276	+0.031	3.76	3.38	0.490	3.87	−0.11	−0.33	4.00	3.30	0.223	3.52	+0.48	+0.02
Control Base-line, Average of Last Three Weeks	14.42	11.45	1.79	13.24	+1.18	0.0	0.920	0.123	0.634	0.757	+0.162	0.0	1.642	0.953	0.444	1.397	+0.245	0.0	3.76	3.02	0.520	3.54	+0.22	0.0	4.00	3.31	0.229	3.54	+0.46	0.0
Immobilization																														
VII	14.42	11.46	2.08	13.54	+0.88	−0.30	0.920	0.162	0.769	0.931	−0.011	−0.173	1.623	0.966	0.501	1.467	+0.156	−0.089	3.76	3.17	0.551	3.72	+0.04	−0.18	4.00	3.72	0.095	3.82	+0.18	−0.28
VIII	14.42	12.80	1.71	14.51	−0.09	−1.27	0.919	0.184	0.596	0.780	+0.139	−0.023	1.656	1.019	0.422	1.441	+0.215	−0.030	3.76	3.31	0.466	3.78	−0.02	−0.24	4.00	3.81	0.111	3.92	+0.08	−0.38
IX	14.42	12.70	1.86	14.56	−0.14	−1.32	0.920	0.206	0.692	0.898	+0.022	−0.140	1.637	1.057	0.460	1.517	+0.120	−0.125	3.76	3.08	0.466	3.55	+0.21	−0.01	4.00	3.67	0.123	3.79	+0.21	−0.25
X	14.42	11.83	1.92	13.75	+0.67	−0.51	0.919	0.204	0.686	0.890	+0.029	−0.133	1.642	0.995	0.469	1.464	+0.178	−0.067	3.76	3.20	0.476	3.68	+0.08	−0.14	4.00	3.72	0.121	3.84	+0.16	−0.30
XI	14.42	12.68	1.75	14.43	−0.01	−1.19	0.920	0.240	0.669	0.909	+0.011	−0.151	1.637	1.049	0.470	1.519	+0.118	−0.127	3.76	3.42	0.474	3.89	−0.13	−0.35	4.00	3.80	0.125	3.93	+0.07	−0.39
XII	14.42	12.21	2.22	14.43	−0.01	−1.19	0.921	0.249	0.822	1.071	−0.150	−0.312	1.621	1.029	0.590	1.619	+0.002	−0.243	3.76	3.17	0.569	3.74	+0.02	−0.20	4.00	3.78	0.088	3.87	+0.13	−0.33
XIII	14.42	12.18	1.75	13.93	+0.49	−0.69	0.921	0.236	0.679	0.915	+0.006	−0.156	1.618	1.034	0.466	1.500	+0.118	−0.127	3.76	2.87	0.419	3.29	+0.47	+0.25	4.00	3.58	0.067	3.65	+0.35	−0.11
Average of Immobilization	14.42	12.27	1.90	14.17	+0.25	−0.93	0.920	0.212	0.702	0.914	+0.006	−0.156	1.633	1.021	0.483	1.504	+0.129	−0.116	3.76	3.17	0.489	3.66	+0.10	−0.12	4.00	3.73	0.104	3.83	+0.17	−0.29
Recovery																														
XIV	14.42	11.87	1.72	13.59	+0.83	−0.35	0.921	0.221	0.664	0.885	+0.036	−0.126	1.618	1.008	0.457	1.465	+0.153	−0.092	3.76	2.95	0.440	3.39	+0.37	+0.15	4.00	3.12	0.121	3.24	+0.76	+0.30
XV	14.42	11.22	1.87	13.09	+1.33	+0.15	0.919	0.203	0.711	0.914	+0.005	−0.157	1.639	0.981	0.493	1.474	+0.165	−0.080	3.76	2.69	0.529	3.22	+0.54	+0.32	4.00	3.34	0.164	3.50	+0.50	+0.04
XVI	14.42	10.78	2.01	12.79	+1.63	+0.45	0.919	0.183	0.803	0.986	−0.067	−0.229	1.639	0.869	0.517	1.386	+0.253	+0.008	3.76	2.62	0.554	3.17	+0.59	+0.37	4.00	3.38	0.170	3.55	+0.45	−0.01
XVII	14.42	9.32	1.68	11.00	+3.42	+2.24	0.919	0.143	0.636	0.779	+0.140	−0.022	1.639	0.829	0.409	1.238	+0.401	+0.156	3.76	2.62	0.453	3.07	+0.69	+0.47	4.00	2.87	0.181	3.05	+0.95	+0.49
XVIII	14.42	9.69	1.77	11.46	+2.96	+1.78	0.919	0.115	0.653	0.768	+0.151	−0.011	1.656	0.841	0.452	1.293	+0.363	+0.118	3.76	2.33	0.560	2.89	+0.87	+0.65	4.00	2.89	0.170	3.06	+0.94	+0.48
XIX	14.42	10.22	2.04	12.26	+2.16	+0.98	0.921	0.115	0.697	0.812	+0.109	−0.053	1.618	0.992	0.487	1.479	+0.139	−0.106	3.76	2.24	0.509	2.75	+1.01	+0.79	4.00	3.16	0.211	3.37	+0.63	+0.17

* Potassium intake and balance figures corrected for additional intake from coffee of approximately 0.25 Gm. daily; these figures are probably accurate within +0.10 Gm.

† Urinary output figures given are for first 3 days of period; during 4th, 5th and 6th days subject was away on leave of absence (death of father); 7th day subject resumed diet and control regimen.

TABLE XIV

METABOLIC BALANCES, SUBJECT S. W., SEVEN-DAY PERIODS—ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen						Calcium						Phosphorus						Potassium						Sodium					
	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake*	Output			Balance*	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line
		Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total		
Control																														
I	14.42	12.84	1.19	14.03	+0.39	−0.21	0.920	0.222	0.629	0.851	+0.069	−0.012	1.639	0.953	0.563	1.516	+0.123	−0.046	3.76	3.00	0.489	3.49	+0.27	+0.15	4.00	3.41	0.026	3.44	+0.56	+0.40
II	14.42	12.48	1.34	13.82	+0.60	0.00	0.920	0.212	0.726	0.938	−0.018	−0.099	1.639	0.995	0.597	1.592	+0.047	−0.122	3.76	3.32	0.463	3.78	−0.02	−0.14	4.00	3.93	0.026	3.96	+0.04	−0.12
III	14.42	12.84	1.20	14.04	+0.38	−0.22	0.920	0.213	0.597	0.810	+0.110	+0.029	1.639	0.989	0.500	1.489	+0.150	−0.019	3.76	3.09	0.432	3.52	+0.24	+0.12	4.00	3.86	0.036	3.90	+0.10	−0.06
IV	14.42	13.08	1.19	14.27	+0.15	−0.45	0.920	0.216	0.597	0.813	+0.107	+0.026	1.653	0.955	0.510	1.465	+0.187	+0.018	3.76	3.14	0.437	3.58	+0.18	+0.06	4.00	4.17	0.020	4.19	−0.19	−0.35
V	14.42	12.68	1.06	13.74	+0.68	+0.08	0.920	0.212	0.626	0.838	+0.082	+0.001	1.623	1.002	0.493	1.495	+0.128	−0.041	3.76	3.33	0.449	3.78	−0.02	−0.14	4.00	3.22	0.028	3.25	+0.75	+0.59
VI	14.42	12.10	1.12	13.22	+1.20	+0.60	0.919	0.210	0.683	0.893	+0.026	−0.055	1.656	0.905	0.543	1.448	+0.208	+0.039	3.76	3.20	0.477	3.68	+0.08	−0.04	4.00	3.97	0.034	4.00	0.00	−0.16
Control Base-line, Average of Last Four Weeks	14.42	12.68	1.14	13.82	+0.60	0.0	0.920	0.213	0.626	0.839	+0.081	0.0	1.643	0.962	0.512	1.474	+0.169	0.0	3.76	3.19	0.449	3.64	+0.12	0.0	4.00	3.81	0.029	3.84	+0.16	0.0
Immobilization																														
VII	14.42	12.93	1.07	14.00	+0.42	−0.18	0.920	0.322	0.593	0.915	+0.005	−0.076	1.624	1.109	0.446	1.555	+0.069	−0.100	3.76	3.56	0.419	3.98	−0.22	−0.34	4.00	3.95	0.008	3.96	+0.04	−0.12
VIII	14.42	15.44	1.16	16.60	−2.18	−2.78	0.919	0.486	0.607	1.093	−0.174	−0.255	1.656	1.197	0.483	1.680	−0.024	−0.193	3.76	3.70	0.350	4.05	−0.29	−0.41	4.00	4.10	0.009	4.11	−0.11	−0.27
IX	14.42	15.04	1.31	16.35	−1.93	−2.53	0.920	0.563	0.769	1.332	−0.412	−0.493	1.637	1.249	0.589	1.838	−0.201	−0.370	3.76	3.28	0.464	3.74	+0.02	−0.10	4.00	3.88	0.017	3.90	+0.10	−0.06
X	14.43	13.56	1.18	14.74	−0.31	−0.91	0.919	0.523	0.660	1.183	−0.264	−0.345	1.642	1.172	0.513	1.685	−0.043	−0.212	3.76	3.44	0.449	3.89	−0.13	−0.25	4.00	4.12	0.022	4.14	−0.14	−0.30
XI	14.42	13.30	1.22	14.52	−0.10	−0.70	0.920	0.577	0.762	1.339	−0.419	−0.500	1.637	1.151	0.517	1.668	−0.031	−0.200	3.76	3.29	0.456	3.75	+0.01	−0.11	4.00	4.02	0.026	4.05	−0.05	−0.21
XII	14.42	12.70	1.32	14.02	+0.40	−0.20	0.921	0.575	0.717	1.292	−0.371	−0.452	1.621	1.151	0.543	1.694	−0.073	−0.242	3.76	3.40	0.440	3.84	−0.08	−0.20	4.00	4.02	0.037	4.06	−0.06	−0.22
XIII	14.42	13.04	1.44	14.48	−0.06	−0.66	0.921	0.561	0.822	1.383	−0.462	−0.543	1.618	1.219	0.586	1.805	−0.187	−0.356	3.76	2.98	0.511	3.49	+0.27	+0.15	4.00	3.88	0.035	3.92	+0.08	−0.08
Average of Immobilization	14.42	13.72	1.24	14.96	−0.54	−1.14	0.920	0.515	0.704	1.219	−0.299	−0.380	1.633	1.178	0.525	1.703	−0.070	−0.239	3.76	3.38	0.441	3.82	−0.06	−0.18	4.00	4.00	0.022	4.02	−0.02	−0.18
Recovery																														
XIV	14.42	12.68	1.22	13.90	+0.52	−0.08	0.921	0.488	0.743	1.231	−0.310	−0.391	1.618	1.069	0.553	1.622	−0.004	−0.173	3.76	2.98	0.417	3.40	+0.36	+0.24	4.00	3.60	0.041	3.64	+0.36	+0.20
XV	14.42	11.47	1.39	12.86	+1.56	+0.96	0.919	0.299	0.829	1.128	−0.209	−0.290	1.639	0.923	0.636	1.559	+0.080	−0.089	3.76	2.82	0.546	3.37	+0.39	+0.27	4.00	3.86	0.023	3.88	+0.12	−0.04
XVI	14.42	9.81	1.43	11.24	+3.18	+2.58	0.919	0.200	0.707	0.907	+0.012	−0.069	1.639	0.754	0.521	1.275	+0.364	+0.195	3.76	2.62	0.419	3.04	+0.72	+0.60	4.00	3.82	0.022	3.84	+0.16	0.00
XVII	14.42	9.62	1.23	10.85	+3.57	+2.97	0.919	0.139	0.657	0.796	+0.123	+0.042	1.639	0.816	0.494	1.310	+0.329	+0.160	3.76	2.88	0.412	3.29	+0.47	+0.35	4.00	3.43	0.019	3.45	+0.55	+0.39
XVIII	14.42	10.28	1.18	11.46	+2.96	+2.36	0.919	0.118	0.527	0.645	+0.274	+0.193	1.656	0.891	0.456	1.347	+0.309	+0.140	3.76	2.35	0.380	2.73	+1.03	+0.91	4.00	3.64	0.030	3.67	+0.33	+0.17
XIX	14.42	10.99	1.15	12.14	+2.28	+1.68	0.921	0.151	0.497	0.648	+0.273	+0.192	1.618	0.905	0.474	1.379	+0.239	+0.070	3.76	2.20	0.374	2.57	+1.19	+1.07	4.00	3.44	0.030	3.47	+0.53	+0.37

* Potassium intake and balance figures corrected for additional intake from coffee of approximately 0.25 Gm. daily; these figures are probably accurate within ±0.10 Gm.

to require even longer for readjustment. The highest serum calcium levels occurred during the first and second recovery weeks. The loss of calcium was still occurring three weeks after mobilization. Of the two subjects studied for six weeks after mobilization, one still showed marked calcium retention at the end of that time.

On the other hand, the impairment in creatine metabolism was repaired within three to four weeks and, in general, most of the physiologic functions appeared to be regained within this period. The basal metabolic rate, muscle strength, the reaction of the circulation to the erect position and the blood volume all returned to control levels in three to four weeks. Certain tests required a longer period for recovery. Exercise tolerance required four to six weeks and girth of the extremities five to six weeks; the reclining pulse rate had not yet returned to pre-rest levels after six weeks.

In conclusion, we wish to emphasize that the undesirable effects of immobilization which have been demonstrated are to be anticipated only in very ill patients or in those who are immobilized due to trauma, surgical procedures, poliomyelitis and similar disease conditions. Only a small percentage of hospital patients are immobilized to the same degree as were the subjects in this experiment. From the results of this study there would seem to be little danger to the average patient from unrestricted bed rest for at least the first two to three weeks. The nitrogen losses, although definite, were not marked; changes in calcium metabolism, muscle mass and strength were not pronounced until after the first two to three weeks; an increased tendency to coagulation of the blood of the general circulation was never demonstrated.

However, for the patient rather rigidly immobilized and forced to remain so for several weeks, there appear to be certain hazards. The threat of urinary tract stone formation, the impaired response of the circulation to the upright position, the derangement in creatine metabolism and loss of muscle mass and strength may become of real concern.

SUMMARY

A study of the effects of immobilization upon various metabolic and physiologic functions of four normal, healthy, young men was carried out on a metabolism ward during control (five to seven weeks), immobilization (six to seven weeks) and recovery (four to six weeks) periods. Throughout the study, dietary intake was kept constant. During the immobilization period the subjects were placed in bi-valved plaster casts extending from the umbilicus to the toes.

1. Nitrogen excretion began to increase on the fifth to sixth day of immobilization and reached its peak during the first half of the second week. Total nitrogen losses ranged from 29.8 to 83.6 Gm., and averaged 53.6 Gm.

2. Both urinary and fecal calcium excretion increased during immobilization, maximum excretion being reached by the fourth to fifth week. Total calcium losses ranged from 9 to 23.9 Gm. The calcium content of the urine was doubled during immobilization. The absence of appreciable increase in urine volume, the slight rise in urinary pH and the failure of urinary citric acid to rise parallel with the increase in calcium would all favor the precipitation of calcium phosphate in the urinary tract. A slight elevation in serum calcium levels occurred at the end of the immobilization period.

3. During immobilization there was an increase in the excretion of phosphorus, total sulfur, sodium and potassium. Total sulfur was excreted in the urine in close correlation from week to week with urinary nitrogen in the ratio in which these elements exist in muscle protoplasm. The changes in phosphorus excretion showed moderately good correlation with the changes in nitrogen and calcium excretion.

4. During recovery there was retention of nitrogen, calcium, phosphorus, sulfur and potassium. The recovery or return to control levels of metabolic functions was slow, retention of nitrogen and phosphorus

continuing for six weeks. Re-stabilization of calcium metabolism appeared to require more than six weeks.

5. Although creatine and creatinine excretion remained fairly constant, there was a definite lowering of creatine tolerance during immobilization. This impairment in creatine metabolism was accompanied by a significant decrease in muscle mass and muscle strength in the immobilized limbs.

6. In only one subject was there a significant lowering of 17-ketosteroid excretion during immobilization; this subject also experienced the largest nitrogen losses.

7. The decline in basal metabolic rate during immobilization averaged 6.9 per cent among the four subjects.

8. Immobilization brought about a deterioration in the mechanisms essential for adequate circulation in the erect position as indicated by an increased tendency to faint in tilt table tests. Experiments indicated that the legs were the principal site of changes responsible for this deterioration and suggested that increased venous engorgement, increased extravascular fluid, capillary fragility and impaired venous or muscle tone play a rôle.

9. Other circulaotry changes brought about by immobilization were a decline in total blood volume averaging 5.4 per cent, marked decreases in exercise tolerance as measured by Master and Schneider tests and an increase in the resting pulse rate of 3.8 beats per minute during immobilization, followed by an additional increase of 4.7 beats per minute during the first three weeks of recovery.

10. The recovery or return to control levels of most physiologic functions required three to four weeks; exercise tolerance and leg girth required four to six weeks and the reclining pulse rate more than six weeks.

11. Changes in body weight during immobilization were small, probably as a result of the simultaneous loss of muscle protoplasm and storage of fat or carbohydrate.

12. There were no significant changes due to immobilization in blood coagulation studies, blood circulation time, heart size, electrocardiograms, resting arterial blood pressure, hematocrits, blood counts, vital capacity, maximum ventilation capacity or breath-holding.

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Experiences in the Management of Subacute Bacterial Endocarditis Treated with Penicillin*

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NUMEROUS reports have been made in the literature concerning the treatment of subacute bacterial endocarditis with penicillin.[1-9] It appears that a majority of the patients with this disease can be cured of their infection if adequate dosage of penicillin is given for an adequate period of time. These results are in dramatic contrast to those achieved with any form of therapy hitherto employed. Recovery rate in sulfonamide-treated patients was at best between 2 and 10 per cent,[3,10] little better than Libman's estimated spontaneous recovery rate of 3 per cent.[11] However, there are still many problems in the diagnosis, treatment and practical management of patients with this disease which are not yet fully understood or appreciated. Clinical recognition of bacterial endocarditis is frequently delayed for many months and bacteriologic diagnosis may be very difficult. Complicating factors such as embolic phenomena, cardiac or renal insufficiency, acute rheumatic fever and sensitivity to penicillin may arise during the course of treatment and profoundly affect the result. The constitution of adequate treatment has not been clearly defined and it becomes quite clear upon reviewing reported failures in treatment that many such patients have not been given adequate amounts of penicillin over a sufficient period of time. Present information concerning the progress and ultimate outcome of patients successfully cured of their infection by penicillin is inadequate. As large statistics obtained under uniform conditions are not yet available, it is hoped that this account of experiences in handling a group of patients with subacute bacterial endocarditis will add something to the present understanding of these problems.

In any consideration of subacute bacterial endocarditis, it is important to point out that one is not dealing with a simple or primary disease process. It is an infection which is superimposed upon an underlying disease or abnormality and the resultant symptoms, physical alterations and clinical course will be the product of both processes. In any given instance, therefore, it may be difficult if not impossible to determine whether some particular clinical feature is due to the subacute bacterial endocarditis alone, or to the underlying process, or to a combination of the two.

CASE MATERIAL

Thirty-five cases constituted the group studied. All were admitted to the wards of the Johns Hopkins Hospital and represent an unselected group of consecutive patients in whom the diagnosis of subacute bacterial endocarditis was established. In addition to the usual supportive measures, penicillin was the only therapy employed. Anticoagulants were not used as there is very little evidence that they are beneficial in the treatment of bacterial endocarditis and there are indications that they may actually be harmful.[1,12,13]

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TABLE I

PERTINENT DATA OF THE CLINICAL COURSE OF THE PATIENTS WHO DID NOT RECOVER

Case No.	Age	Sex	Race	Duration of Symptoms before Penicillin Treatment	Organism and Sensitivity (units per cc.)	Valve Involved	Daily Penicillin Dosage	Method of Administration	Total Days of Penicillin Treatment	Total Units of Penicillin, Million	Complications	Outcome of Treatment
1	47	M	C	12 days	Streptococcus equinus 0.06	Tricuspid	320,000 × 10 1,200,000 × 10 1,240,000 × 4 2,240,000 × 9 3,600,000 × 28	Intramuscular Intramuscular Intramuscular Intramuscular Intramuscular	61	153	Persistent bacteremia during first four courses; sensitivity decreased from 0.06–1.0; moderate degree renal impairment; improved greatly on fifth course of penicillin when suddenly developed abdominal pain and shock; death followed	Autopsy: Heart slightly enlarged; tricuspid valve scarred and covered with vegetations; pulmonary arteries filled with emboli from tricuspid valve; extensive hemorrhagic pancreatitis
2	28	F	W	5 mo.	Alpha streptococcus	Mitral	300,000 × 10 280,000 × 7	Intravenous Intramuscular	17	5	Improving when suddenly developed upper abdominal mass, became cyanotic and comatose	Autopsy: Heart slightly enlarged; myocardium studded with many small abscesses; mitral valve thickened and covered with vegetations. Aschoff bodies present; splenic infarct; small abscesses in kidneys; ruptured mycotic aneurysm of superior mesenteric artery
3	14	F	C	3 mo.	Streptococcus mitis 0.036	Mitral aortic	320,000 × 14	Intramuscular	14	4.2	Having satisfactory response when therapy was interrupted for blood cultures; developed progressive cardiac failure, azotemia and jaundice	Autopsy: Heart greatly dilated and hypertrophied; mitral and aortic valves distorted with vegetations. Aschoff bodies present; marked CPC of liver with central necrosis; mycotic aneurysm of cerebral artery
4	11	F	W	5 wk.	Streptococcus mitis	Mitral	600,000	Intramuscular	26	15.6	End of first week of treatment subarachnoid hemorrhage, followed two weeks later by a second fatal episode	Autopsy: Moderate enlargement of left ventricle; mitral valve distorted, covered with vegetations; atelectasis of left lung with mucus plug; subarachnoid hemorrhage, source not evident
5	17	F	C	9 mo.	Gram-negative anaerobic Coccobacillus ? Bacteroides	Mitral tricuspid	1,200,000	Intramuscular	9	10.8	Improved, but therapy was halted for more blood cultures; developed severe progressive cardiac failure, hematuria and azotemia	Autopsy: Vegetations on mitral and tricuspid valves and wall of left auricle with some healing; infarcts in spleen and kidneys
6	23	F	C	1 mo.	Streptococcus fecalis 8.0	Mitral aortic	600,000 × 2 1,200,000 × 6	Intramuscular	8	9	Persistent bacteremia, acute cardiac failure and death	No autopsy

7	25	F	W	6 mo.	Streptococcus fecalis 1.06	Aortic	400,000 × 6 2,400,000 × 6 5,000,000 × 16 5,000,000 × 40	Intramuscular Intramuscular Intravenous	68	295	Persistent bacteremia with sensitivity decreasing to 6.25 units, recovered from subarachnoid hemorrhage; spleen filled with multiple abscesses which were removed but bacteremia continued	Died at home three months after discharge
8	25	F	W	5 mo.	Streptococcus mitis	Mitral	300,000 × 10 240,000 × 30	Intravenous Intramuscular	40	10.3	First course halted because of incipient cardiac failure; bacteremia recurred and continued; developed left hemiplegia and infarcts to spleen and kidneys	Died at home shortly after discharge
9	39	M	W	6 mo.	Streptococcus salivarius	Mitral	200,000 × 21 400,000 × 21 400,000 × 12 200,000 × 23	Intravenous Intramuscular Intravenous Intramuscular	77	23	Bacteremia continued; emboli to spleen, kidneys and brain; treatment sporadic because of scarcity of penicillin	Died at home shortly after discharge
10	22	M	W	5 mo.	Streptococcus ignavus	Aortic mitral	240,000	Intramuscular	21	5	Cultures became sterile but there were continued fever, sweats, tachycardia, hematuria and moderate depression of renal function; penicillin halted after splenic and cerebral embolus which developed	Died in coma with progressive cardiac failure
11	57	M	W	2 mo.	Streptococcus salivarius	Aortic mitral	200,000	Intramuscular	8	1.4	Before penicillin started developed acute pulmonary edema and diastolic murmur at aortic area; believed to have ruptured aortic leaflet	Autopsy: Heart moderately enlarged; small areas of necrosis in myocardium; fresh vegetations on mitral, aortic valves and auricular surface; 5 × 5 mm. rupture of one aortic cusp; marked degree healing of valves; infarcts of spleen and kidneys
12	27	M	W	6 wk.	Alpha streptococcus	Aortic mitral	1,200,000 × 21 1,800,000 × 2 2,400,000 × 2 4,800,000 × 4 9,600,000 × 4	Intramuscular	33	84	Cultures became sterile but continued febrile; developed progressive cardiac failure; two episodes of pulmonary embolism; terminal azotemia	Autopsy: Heart greatly enlarged; mycotic aneurysm of coronary artery with myocardial infarction; fresh vegetations imposed upon old, healed, calcified endocarditis of a bicuspid aortic valve and fresh vegetations also on mitral; infarcts in spleen and kidneys
13	44	M	W	4 mo.	Streptococcus salivarius 0.045	Mitral	1,200,000 × 12	Intramuscular	12	14	Sudden onset of precordial pain with death following	Autopsy: Extreme sclerosis of coronary arteries with coronary thrombosis and myocardial infarction; active rheumatic fever; organizing vegetations on mitral valve; splenic infarct

TABLE II

PERTINENT DATA OF THE CLINICAL COURSE OF PATIENTS WHO RECOVERED

Case No.	Age	Sex	Race	Duration of Symptoms before Penicillin Treatment	Organism and Sensitivity (units per cc.)	Valve Involved	Daily Dosage of Penicillin	Method of Administration	Total Days of Penicillin Treatment	Total Units of Penicillin, Million	Complications	Outcome of Treatment	Follow-up Period
14	34	F	W	4 mo.	Alpha streptococcus	I.V. septal defect	250,000	Intravenous	14	3.5	None	Well	36 mo.
15	46	M	W	14 mo.	Bacteroides 1.6	Mitral	600,000 × 6 1,200,000 × 57	Intramuscular	63	73	Moderate depression renal function	Well for five months, then rapidly went into cardiac and renal failure and died; autopsy; rheumatic scarring of mitral and aortic valves, completely healed and calcified erosion of mitral; infarction of right lower lung from mural thrombus right heart; infarction spleen; very extensive interstitial nephritis	5 mo.
16	25	F	W	4 mo.	Alpha streptococcus salivarius	Patent ductus arteriosus	240,000	Intramuscular	30	7.2	Pulmonary embolus lower left lung ten days after treatment started; ductus ligated	Well	24 mo.
17	28	F	C	2 mo.	Alpha streptococcus salivarius 0.045	Mitral	1,200,000	Intramuscular	42	50	None	Well Two months pregnant	7 mo.
18	23	M	W	3 wk.	Gram-negative anaerobic Coccobacillus ? Bacteroides 0.29	Mitral	400,000 × 6 1,200,000 × 14	Intramuscular	20	20	None	Well	18 mo.
19	26	F	W	7 mo.	Alpha streptococcus ignavus	Mitral, aortic	1,200,000 × 35 800,000 × 22	Intramuscular	57	60	None	Well but for mild dyspnea	5 mo.
20	26	F	W	3 mo.	Alpha streptococcus	Mitral	200,000	Intramuscular	21	4.2	Paroxysmal auricular fibrillation	Well until four months after discharge when cultures were again positive for alpha streptococcus. Treated with 7.2 million units of penicillin over twenty-one day period. Well since then	20 mo.
21	44	M	W	5 mo.	Alpha streptococcus mitis 0.0039	Aortic	400,000 × 35 1,200,000 × 21	Intramuscular	56	39	Before treatment started embolus to left superior cerebellar artery; at completion of thirty-five day course of penicillin bacteremia recurred	Well	5 mo.

22	19	F	C	1 mo.	Streptococcus salivarius -	Mitral	240,000	Intramuscular	21	5	None	Well	26 mo.
23	24	F	W	2 mo.	Alpha streptococcus	Mitral	300,000	Intravenous	14	4.2	None	Well	36 mo.
24	32	F	W	6 mo.	Streptococcus salivarius	Aortic, mitral	300,000 × 14 300,000 × 10 300,000 × 20	Intravenous Intravenous Intravenous	44	13.2	Had two recurrences of bacteremia six days after first course and nine days after second; remained sterile after third	Well but for mild dyspnea	28 mo.
25	42	F	W	3 mo.	Alpha streptococcus	Mitral	300,000 × 14 280,000 × 20	Intravenous Intramuscular	34	10	Had recurrence of bacteremia nine days after first course	Well but for mild dyspnea	29 mo.
26	35	M	W	1 mo.	Streptococcus mitis 0.056	Mitral	1,200,000	Intramuscular	29	34.8	None	Well	12 mo.
27	25	F	C	6 mo.	Streptococcus mitis	Mitral	320,000	Intramuscular	13	4.2	None	Well but for moderate dyspnea	32 mo.
28	18	F	C	6 mo.	Alpha streptococcus	Mitral	300,000 × 9 240,000 × 12	Intravenous Intramuscular	21	5.4	None	Well	30 mo.
29	14	M	C	3 mo.	Streptococcus equinus 0.0312	Mitral	240,000 × 4 400,000 × 10 1,200,000 × 50	Intramuscular Intramuscular Intramuscular	70	58.6	Persistent recurrence of bacteremia during first two courses of treatment; two weeks after start of third course had a subarachnoid hemorrhage	Well but for poor vision of right eye	Inadequate
30	70	M	C	2 mo.	Streptococcus salivarius 0.0312	Mitral, aortic	400,000	Intramuscular	23	9.2	None	Well	Died in The State Mental Hospital six months after discharge. Cause ?
31	23	F	C	8 mo.	Alpha streptococcus	Mitral	1,200,000	Intramuscular	47	56.4	None	Well	5 mo.
32	25	F	W	7 mo.	Alpha streptococcus mitis 10.00	Mitral, aortic	4,800,000	Intramuscular	42	201.0	Continued minor embolic episodes throughout course	Well but for mild dyspnea on moderately restricted activity	7 mo.
33	22	F	W	24 mo.	Negative	Patent ductus aortic	1,200,000 × 8 4,800,000 × 35	Intramuscular	43	177	After first course of penicillin fever continued; complete defervescence after increased dosage; patent ductus ligated twenty-fifth day; afterward signs of a.i. more marked; evidence of considerable renal and hepatic damage	Well but for persistent pendant edema	5 mo.
34	18	F	W	2 mo.	Alpha streptococcus	Mitral	1,200,000 × 11 3,600,000 × 9 7,200,000 × 35	Intramuscular Intramuscular Intramuscular	54	297	Embolus to spleen	Well	4 mo.
35	42	M	W	31 mo.	Streptococcus salivarius 6.2	Mitral	1,200,000 × 10 12,000,000 × 7 3,500,000 × 15 12,000,000 × 12 18,000,000 × 14 18,000,000 × 42	Intramuscular Intramuscular Penicillin in oil and beeswax Intramuscular Intramuscular Intravenous	100	1,450	Continued evidence of infection until massive dosages employed; on thirty-fifth day embolus to spleen and brachial artery and on eighty-fourth day embolus to spleen. Thighs and buttocks abscessed from intramuscular administration of penicillin	Well on discharge but has developed progressive cardiac enlargement and increasing cardiac failure	3 mo.

Symptoms. The symptoms presented by this group of patients are conveniently considered under three headings: (1) those secondary to bacterial infection; (2) those secondary to embolism and (3) those secondary to cardiac disease. In Tables I and II some of the pertinent data of the clinical course of these patients are summarized.

Of the three groups, symptoms arising from infection were by far the most common. The disease almost always manifested itself insidiously so that it was sometimes many months before the patients recognized that their health was seriously affected. In many instances, mild feverishness was the only early symptom. Frank chills did not often accompany the feverishness but sweats and weakness frequently did. An appreciable loss of weight was noted by twelve patients. Joint pains, usually transitory and without marked local reactions, were present in about one-half of the group. In some instances, their presence could be ascribed solely to the bacterial infection while in others the possibility of a concomitant active rheumatic fever had to be considered. Vague musculoskeletal aching was mentioned less often. It is of some interest that the complaints of feverishness, weakness and musculoskeletal aching had led to the diagnosis of grippe in eight patients.

The occurrence of embolism was responsible for the major symptoms of eight patients. Two of these had a cerebral embolus, two developed temporary blindness, two had an embolus to an extremity and the remaining two had emboli to the spleen and kidney respectively. Eight patients noted petechiae in their skin or mucous membranes and a small group told of soreness in the tips of their fingers or toes or of small areas of transitory swelling and tenderness in the soft tissues of the extremities.

Only a small number of patients had complaints indicative of cardiorespiratory difficulty. This confirms the rather important point that patients who develop subacute bacterial endocarditis frequently have only a minimal degree of cardiac disease. Fully two-thirds of our group of patients had either no history of heart disease or if evidences of heart disease were present they were minimal. Only ten patients had recognized cardiac disease at the time their illness began.

Physical Examination. Weight loss and pallor were the most commonly encountered physical alterations, being present in almost all of the patients. Petechiae were observed in over 50 per cent of the group and there was a similar incidence of splenic enlargement. It is perhaps wise to emphasize the converse of this statement, pointing out that in almost one-half of these patients with proven subacute bacterial endocarditis the spleen was never felt and petechiae were never seen. The liver was believed to be enlarged in seventeen instances. Only one-third of the patients had clubbing of the fingers or toes while tenderness of the toes and fingers was present in but a few individuals. Seven patients had evidences of an acute arthritis. In many of the patients, the heart was thought to show some degree of enlargement although this clinical impression was not always confirmed by teleoroentgenogram. Evidences of frank cardiac failure were observed in only eight of the patients. One patient had auricular fibrillation.

The mitral valve was most frequently involved by the endocardial infection, twenty patients being considered to have only a mitral lesion, while a combined mitral and aortic valvulitis was present in nine instances. Two individuals were found at post-mortem to have vegetations on the tricuspid valve which had not been suspected previously. Two patients had a patent ductus arteriosus and one a patent interventricular septum.

Laboratory Findings. A mild hypochromic anemia was usually present. It was seldom very marked. The white blood count was elevated in only a few instances. In view of the common impression that microscopic hematuria is a frequent and characteristic finding in subacute bacterial endocarditis, it is worth pointing out that fifteen of our patients never developed this finding although

the urine was examined on repeated occasions. The incidence of albuminuria and of white blood cells in the urine paralleled that of hematuria. The results of renal function tests will be discussed at another point.

In all but one instance, an organism was isolated from the blood stream and a positive blood culture was obtained from this individual at another hospital prior to admission and inception of treatment here. The penicillin sensitivity of these organisms was determined in only one-half of the group and ranged from 0.0039 to 10 units.

Great care should be employed in carrying out bacteriologic examinations. Both aerobic and anaerobic cultures should be inoculated. Cultures should be taken at frequent intervals. They should be retained and reviewed for a period of not less than three weeks before they are considered sterile. In several of these cases, the cultures did not show any detectable growth until the second week and in one instance not for twenty-one days. When the diagnosis of subacute bacterial endocarditis seems reasonably certain from a clinical standpoint and yet there is difficulty in obtaining bacteriologic confirmation, mycotic organisms as well as unusual bacteria such as the genus Bacteroides should be searched for. There were three cases due to the latter organisms in this group of patients and the isolation of the organisms depended upon long incubation of the cultures anaerobically.

Clinical Course. The majority of our patients were given penicillin by intermittent intramuscular injection usually at intervals of two hours. Although this mode of administration has well recognized disadvantages, in the main it proved to be the most practical and the least distressing to the patient. However, there were instances in which such severe reactions developed at the point of injection that a change to continuous intravenous administration was made. This technic was also used in a few individuals infected with a highly resistant organism for in such instances it was not feasible to achieve adequate penicillin levels by the intramuscular route. Repeated venous thrombosis was the principal drawback to this method.

The immediate response to penicillin treatment was very striking when the dosage was adequate and when no complications appeared. Blood cultures usually became sterile within one to two days and rarely later than four to five days. Defervescence occurred customarily within three to four days with a concomitant fall in pulse rate. At the same time the patients rapidly developed a sense of well being, the sweats and anorexia steadily vanishing. Although gain in weight and elevation of the hemoglobin and red count were progressive, several weeks were required before normal values were reached. No significant alteration in the white blood count was noted as generally the admission count was normal or a little depressed. In the few instances in which the white blood count was elevated before treatment, a rapid fall to normal took place. In several instances, the sedimentation rate was still elevated at the time therapy was completed despite the fact that all other criteria indicated a successful result. In a few instances, embolic phenomena continued to occur many weeks after the institution of apparently adequate therapy. As isolated occurrences, they were not believed necessarily to be evidences of inadequate treatment.

In the successfully treated group, cardiac function was not appreciably altered during the course of therapy. There was a subsidence of the initial overactivity which was so characteristic upon admission. One patient developed a paroxysm of auricular fibrillation and another several episodes of auricular tachycardia. There were no significant changes noted in the size of the heart. There were no indications of progressive valvular damage except in one instance in which signs of aortic insufficiency appeared during the treatment of a young girl following ligation of an infected patent ductus arteriosus.

Reference has already been made to the fact that a large number of these patients

showed no evidence whatever of renal involvement. In most instances, a mild hematuria and albuminuria were the only evidences of renal implication. Following treatment, these generally disappeared and of the group who made an apparent recovery from endocarditis only two patients manifested depression of renal function while another continued to have a trace of albumin and a few red blood cells in his urinary sediment.

Complications Arising During Therapy. Complications which arose during the course of treatment of these patients can best be grouped and considered under the following headings: (1) those associated with cardiac failure; (2) those associated with embolism; (3) those associated with persistent bacteremia and (4) miscellaneous.

In analyzing the occurrence of these complications, an attempt will be made to relate them to the adequacy or inadequacy of the treatment received. As will be made clear in the discussion, experience in treating this group of patients has altered our concept of "adequate treatment." It has become clear upon review that several of the patients originally considered adequately treated because they were receiving dosages commonly regarded as sufficient (500,000 units daily for three to four weeks)[14] were in fact inadequately treated in the light of additional experience.

Frank cardiac failure occurred in eight individuals. In two instances, therapy was considered adequate while in five it was deemed inadequate. Severe heart failure ending fatally developed in one individual after rupture of an aortic cusp prior to institution of therapy. Of the two patients who developed cardiac failure while receiving adequate treatment, one was found at post mortem examination to have a myocardial infarction secondary to a mycotic aneurysm of one of the coronary arteries while the other was found to have a myocardial infarction secondary to thrombosis of an extremely sclerotic coronary artery. In addition, this latter patient also had rheumatic myocarditis. Three of the patients receiving inadequate treatment were believed to have rheumatic myocarditis and in two instances this impression was confirmed at postmortem. The other two patients developed cardiac failure during the course of a severe Streptococcus fecalis endocarditis which was resistant to treatment. But for these latter cases, it would seem difficult to relate the onset of cardiac failure to inadequate treatment alone and one must conclude, therefore, that in a certain number of patients myocardial insufficiency will occur during the course of subacute bacterial endocarditis regardless of the amount of penicillin employed. This is attributable to the dual nature of the disease process. Although penicillin may be successful in abolishing the bacterial endocarditis, it cannot be expected to alter the underlying cardiac abnormalities which may be responsible for the continued illness or ultimate death of the patient.

Complications Arising from Embolism. The occurrence of emboli to the brain, lungs, kidneys, spleen and peripheral arteries was much more frequent in patients receiving inadequate therapy, eleven of such patients having major embolic episodes as opposed to only three who were undergoing adequate treatment. One patient had a cerebral embolus just before treatment was instituted. Attention has already been drawn to the fact that in a few instances emboli continued to occur many weeks after adequate therapy was begun, one individual having a splenic infarction eighty-four days after commencement of treatment. The suggestion has been made that the institution of penicillin treatment may be responsible for a transient increase in the incidence of embolism as a result of the healing and organization of the affected endocardium. The fact that ten patients gave a history indicative of embolism prior to the reception of any therapy as contrasted to fourteen patients in whom emboli occurred after treatment was started, while far from conclusive, would make it seem improbable that such an impression was valid. The only conclusion which can be drawn from

our experience is that the administration of adequate amounts of penicillin appears to decrease appreciably the occurrence of major embolism.

Persistent Bacteremia. A persistent or recurrent bacteremia was present during the course of treatment of six patients. As would be anticipated, none of these patients was receiving adequate treatment when this occurred. Two of these infections were due to highly resistant strains of Streptococcus fecalis and although moderately large dosages of penicillin were used no response was obtained. They were listed as inadequately treated because no attempt was made to employ massive penicillin therapy such as was found to be effective in other highly resistant infections. However, it is quite clear that a more effective antibiotic agent is needed to combat Streptococcus fecalis endocarditis. A recurrent bacteremia occurred twice during the course of treatment of one patient and three times in the course of another. In all instances, there was a satisfactory response to penicillin once adequate dosage was established and there was nothing to indicate that subeffective dosages of penicillin had increased significantly the bacterial resistance of the organisms in these cases.

Miscellaneous Complications. Azotemia and reduced renal function were important complications encountered in seven patients. Three of this group were found at autopsy to have renal infarctions and infarctions were also found in a fourth when a nephrectomy was done subsequently to remove a functionless kidney. The kidneys of another patient at autopsy revealed many hyalinized glomeruli, extensive interstitial infiltration and atrophy, and disappearance of tubules and scarring. The sixth in the group, although apparently recovering from the infection, had at the time of discharge a phenolsulfonphthalein excretion of 35 per cent and a urea clearance of 35 per cent with inability to concentrate the urine above 1.018. The last patient died with evidence of progressive renal impairment but the exact nature of his nephritis was not determined. In none of these instances was there any apparent correlation between the development of renal complications and the adequacy of treatment nor did the length of time the infection had existed untreated seem to be significant.

One patient developed a marked degree of icterus terminally and autopsy disclosed severe chronic passive congestion with marked central necrosis of the liver. Another patient was found at autopsy to have extensive hemorrhagic pancreatitis which had not been suspected during life. The endocardial infection was not thought to have played a part in its causation.

Particular note should be made of a relatively minor but none the less important complication which occurred in two patients. A marked inflammatory reaction with necrosis of the muscles developed at the sites of penicillin injection, associated with moderate elevation of the temperature and general malaise. For a short time this systemic reaction was misinterpreted as evidence of reactivation of the endocarditis.

Results of Treatment. The overall mortality of this group of thirty-five patients with subacute bacterial endocarditis was 37 per cent. However, when nine patients whose treatment was considered to be definitely inadequate were omitted from the series, the mortality was reduced to 20 per cent. Thus, 80 per cent of the patients given adequate therapy recovered from the infection.

It is of interest to compare the apparent causes of death of the adequately and inadequately treated patients. Of the adequately treated group, the pulmonary arteries of one individual were found at autopsy to be filled with emboli originating from vegetations on the tricuspid valve. Another patient had a massive subarachnoid hemorrhage. The remaining two patients had extensive myocardial infarction, in one instance due to occlusion of a sclerotic coronary artery and in the other secondary to a large mycotic aneurysm of one of the coronary vessels. The important observation was made at autopsy that all

four of these patients showed evidence of an active bacterial endocarditis, and this in spite of therapy which had been considered adequate by clinical criteria. Only one of the group showed evidence of active rheumatic myocarditis. The death of six of the nine inadequately treated patients was attributed to cardiac failure. Three of these were thought at autopsy to have acute rheumatic myocarditis and, in addition to this, the myocardium of one individual was studded with multiple small abscesses. Another of the group was found to have a ruptured aortic cusp. Four of these patients had a persistent bacteremia and two of them had multiple emboli to the brain, spleen and kidneys. The last patient in the group died following rupture of an aneurysm of the superior mesenteric artery. Again, it is important to point out that all but one of this group manifested at the time of death an active bacterial endocarditis, either by the presence of persistently positive blood cultures or by the findings at autopsy examination.

In considering the causes of death in the adequately and inadequately treated patients, one is struck by the fact that, but for the instances of rheumatic myocarditis and of myocardial infarction secondary to coronary sclerosis, the deaths are all attributable at least indirectly to a persistence of the bacterial infection. This conclusion is self-evident in those patients who had a continuation of bacteremia and highly probable in those who died as a result of embolism which we have noted is of more frequent occurrence when therapy is inadequate. Thus, the two major causes of death in this group of patients were the character of the underlying cardiac disease and a persistence of the bacterial endocarditis. Several of these patients might have been saved had the antibiotic treatment been more intensive.

Age, sex and race could not be said to have an important influence upon the results of therapy. There was some indication that a long interval of time between onset of symptoms and commencement of treatment was more likely to result in cardiac insufficiency than was a short interval. However, there were several exceptions, individuals with very long-standing infections having an entirely successful response to treatment. Eight patients had been given one or more courses of inadequate treatment at another hospital prior to admission. The organisms of five of this group were found to be more resistant than average but this apparent decreased sensitivity did not militate against a successful recovery of three of the patients who were given large dosages of penicillin. The other two who received inadequate treatment died. It would seem, therefore, that while one or more courses of ineffective treatment may give rise to more highly resistant strains of organisms, such infections can still be overcome provided an adequate amount of penicillin is given.

There was nothing found in this study to indicate that the particular valve involved by the bacterial endocarditis made a difference in the result. Two of the four adequately treated patients who died were found to have vegetations on the mitral valve alone, one showed involvement of both aortic and mitral valves, and the fourth involvement of the tricuspid valve.

The Streptococcus fecalis manifested the highest degree of penicillin resistance, a resistance which became progressively greater as treatment progressed. Both patients infected with this organism died. However, as already pointed out, neither of these patients was given the massive amounts of penicillin which were later found effective in relatively resistant infections.

Thus, in reviewing the results achieved in treating this series of patients, it becomes apparent that success or failure was determined principally by the character of the underlying disease process and of the adequacy of treatment given. While other factors undoubtedly play a part, the major therapeutic concern is that adequate penicillin be given for a sufficient period of time and prior to the development of unalterable cardiac abnormalities.

Follow-up. While it has become apparent that penicillin is a very effective agent in overcoming the infection in most cases of bacterial endocarditis, little is known as yet about the progress of such "cured" patients over a period of years. To what extent does eliminating the infection cure the patient and return him to health? What residuals does a successfully treated subacute bacterial endocarditis leave and to what degree do they interfere with normal cardiac function? Only a post-treatment observation period of long duration can give satisfactory answers. The problem is clearly complicated by the difficulty of estimating how much disability has been produced by the bacterial infection and how much by underlying disease processes. Twenty of the twenty-two patients who were seemingly cured of their infection have been adequately followed since discharge from the hospital. Eight were followed for a period less than six months. During this period four individuals remained entirely well while one complained of mild exertional dyspnea and another has developed progressive cardiac enlargement and symptoms of increasing myocardial failure. One died. He was a forty-six year old white male who was given 73,000,000 units of penicillin over a period of sixty-three days in treatment of a Bacteroides infection of the mitral valve with what appeared to be a complete recovery. His course had been complicated by moderate depression of renal function. Following discharge, he got along well on limited activity until five months had elapsed when he rapidly developed signs and symptoms of myocardial and renal insufficiency and died in acute pulmonary edema with azotemia. Post mortem examination revealed scarring of the mitral and aortic valves due to rheumatic fever. There was an entirely healed erosion with calcification of one cusp of the mitral valve with no evidence of an active bacterial endocarditis. In addition, there was an infarction of the right lower lobe of the lung thought secondary to embolism arising from mural thrombi found in the right side of the heart. Infarcts were also present in the spleen. There was an extensive interstitial nephritis which has already been described. Death was thought due to heart failure and pulmonary infarction. Three patients were followed from six to twelve months, one having mild dyspnea on exertion and the others remaining well. Two individuals were well after a period of eighteen to twenty-four months. Seven patients have been observed from twenty-four to thirty-six months. Four are free of symptoms while three complain of mild exertional dyspnea. Special mention should be made of the only post-treatment recurrence which occurred in the entire series. The patient was a twenty-six year old white female with an undifferentiated alpha-streptococcal infection of the mitral valve who was initially given 4,200,000 units of penicillin over a twenty-one-day period with apparent complete subsidence of infection. However, four months later she again became symptomatic and blood cultures showed growth of an alpha-streptococcus. Alpha-streptococcus was also grown from the socket of an abscessed tooth which was extracted. She was then given 7,600,000 units of penicillin over a twenty-one-day interval with clearing of the infection and she appeared to be well, except for mild exertional dyspnea, when seen twenty months later. Thus, in the twenty patients considered cured of their infection and adequately followed over an interval of three to thirty-six months, there was only one death and one recurrence of infection (or perhaps reinfection), both occurring within six months after completion of therapy. Another patient is showing progressive cardiac enlargement and insufficiency. More than one-half the remainder are entirely well and the rest have evidences of only mild to moderate cardiac insufficiency.

COMMENTS

The importance of early diagnosis now that effective treatment is available is obvious. Although a successful therapeutic result may be achieved despite a long

lapse of time between the onset of the disease and the commencement of treatment, continuation of the infection may result in irreparable damage to the heart or kidneys or allow the occurrence of fatal emboli. The sooner the infection can be brought under control the better the patient's chances for a complete recovery. The diagnosis of subacute bacterial endocarditis is oftentimes a difficult one to make. The classic features of the disease are frequently absent and the presenting manifestations may lead one to suspect a variety of other illnesses. The symptoms arising from the infection have a non-specific character and one may easily misinterpret their true significance unless there is a high index of suspicion of subacute bacterial endocarditis. Embolic occurrences may be distracting and may lead the observer far afield from the true cause of the patient's malady. The evidences of cardiac disease may be minimal. While the physical changes may suggest an endocardial infection, the abnormalities are often not characteristic of the disease and the true nature of the illness may be obscure despite a meticulous physical examination. The diagnosis of subacute bacterial endocarditis can be made at an early date only when the observer appreciates the serious implications of a persistent, unexplained fever in any patient with congenital or valvular heart disease and the proper bacteriologic studies are performed.

The goal of any therapeutic regimen is the cure of the maximum number of patients and not the determination of the smallest amount of an agent which will be effective in the majority of the cases. With this idea in mind, the present concepts of what constitutes adequate treatment of subacute bacterial endocarditis should be reviewed. There can be no doubt of the efficacy of penicillin therapy in the treatment of this disease when it is caused by organisms sensitive to this antibiotic. The chief problem is to determine a program of treatment with penicillin which will be successful in curing the maximum number of patients. It is quite likely that such a program might entail overtreatment in a few instances but, until means are at hand of singling out such particular cases, the only safe plan to adopt is one which will be successful even against the most resistant infections. Certainly at the present time, there is no entirely satisfactory way of determining before treatment how readily a particular patient can be cured of his infection. Hence, it does not seem extravagant to overtreat some patients in order to assure adequate treatment for all. As has been stated, 80 per cent of the patients who were adequately treated recovered from their infections while inadequate therapy was found to be one of the major causes of death in this series. It cannot be overemphasized that evidence of active bacterial endocarditis was found upon autopsy examination of three of the patients who died while receiving treatment which was regarded as adequate. It is therefore apparent that one should critically appraise present criteria of therapeutic adequacy.

Our experiences led us to adopt 100,000 units given intramuscularly every two hours as the basic treatment schedule. This regimen was amplified by increasing amounts of penicillin as seemed warranted by individual circumstances.

Several factors seemed to be of importance in determining the effective penicillin dosage. Of these, the penicillin sensitivity of the organism was of help in affording an approximation of the penicillin level which would be required to achieve a successful result. However, too much confidence could not be placed in this single factor. As now performed *in vitro*, this test does not accurately reduplicate conditions *in vivo* and the results may be misleading. A few of our patients infected with organisms which were thought to be highly resistant had an excellent response to average therapy and the opposite was also true. Sterilization of blood cultures was also of only limited value for this was usually readily achieved and at times in the face of obvious evidences of continued infection. The concentration of penicillin in the blood required to affect

the organisms present in the vegetations on the heart valve may be considerably greater than that required to render the blood stream free of bacteria. It becomes obvious that reliance cannot be placed on the results of laboratory examination alone as the determinants of penicillin requirements. The best indication of effective therapy proved to be a return of temperature and pulse to normal, gain in weight, absence of sweats, the sense of well being of the patient, the subsidence of embolic phenomena, elevation of the red count and hemoglobin toward normal. Thus, it is only by clinical observation of the patient's general condition that one can satisfactorily determine whether or not an established regimen is adequate.

The sensitivity of the infecting organism having been determined, patients were started upon a therapeutic regimen which was calculated to afford a constant penicillin blood level several times greater than the *in vitro* sensitivity. To just what extent the blood levels should exceed the *in vitro* sensitivity in order to produce maximal therapeutic effectiveness is still an unsettled question. We attempted to maintain a level five times the sensitivity and this appeared to be quite adequate.

Once a patient had been started upon a penicillin regimen determined in this manner, his course was followed closely from day to day and if there was failure to achieve any of the effects mentioned above as indications of therapeutic effectiveness, appropriate daily increments of penicillin dosage were given. This process was continued until a satisfactory response was obtained. In one instance, 20,000,000 units a day were given before the results were deemed satisfactory. In those instances in which there was no determination of *in vitro* bacterial sensitivity, the initial dosage was 1.2 million units a day. Thus, the determination of adequate penicillin dosage in subacute bacterial endocarditis is to a certain extent a matter of clinical trial and error. Chief reliance in gauging the adequacy of any given treatment schedule should be placed upon the general condition of the patient and not upon such factors as bacterial sensitivity or penicillin blood levels. Such a scheme of dosage, based primarily upon clinical evidence of satisfactory response, will at times entail the administration of massive amounts of penicillin but we are convinced that only by so doing can one save patients who might otherwise be lost through employment of a more conservative dosage plan. The patient in this series who recovered after receiving 1,450,000,000 units of penicillin is a case in point.

When treatment has been started and all clinical evidences of active infection have disappeared, it is extremely difficult to know when a cure has been effected and treatment may be halted. Within certain limits of dosage, the duration of treatment is just as important as the total amount of penicillin given each day. Using a total dose of 5,000,000 units given in courses lasting five, ten and twenty days, Christie[2] has shown that the percentage of cures was 0, 25 and 50 per cent respectively. On the other hand, when the duration of treatment was uniformly twenty-eight days and the daily dosages were 100,000, 250,000 and 500,000 units, recovery rates were 43, 51, and 61 per cent respectively. Premature discontinuance of treatment may therefore result in failure regardless of the daily quantity of penicillin employed. It is true, as has been mentioned, that a recurrence of bacteremia does not necessarily militate against a successful outcome following an additional course of treatment. The development of a significant increase in bacterial resistance in subacute bacterial endocarditis is apparently unusual.[1,2] But as we have seen, continuance of infection means that there is much more opportunity for the development of irreparable cardiac and renal damage and for the occurrence of embolism which may be fatal. It is impossible at the present time to set a time limit for the administration of penicillin but the experience of finding evidence of continued bacterial infection in patients thought to have been treated for an adequate period

(four to five weeks) has led us to the belief that therapy should be continued over a period of at least two months after all evidences of active infection have subsided.

Commencement of penicillin treatment at an early date is of obvious importance. Should one, therefore, wait for establishment of a definite diagnosis by positive blood cultures? As has been pointed out, bacterial confirmation may require three or four weeks. Three of the early cases in our series clearly demonstrate what may happen during such a delay. In one patient, rupture of the aortic valve led to acute cardiac failure and death before treatment was begun. In the other two instances, penicillin administration was interrupted to obtain further cultures when those taken before therapy had failed to reveal an organism. The patients developed an exacerbation of the infection with progressive cardiac insufficiency and died.

On the other hand, initiation of treatment when one has no knowledge of the responsible organism and its sensitivity to various antibiotic agents has its disadvantages and dangers. Once the patient has been committed to a course of penicillin therapy, he is due for an experience which is going to be both expensive and unpleasant. Drug sensitization may ensue. Furthermore, the premature use of the drug may obscure the clinical picture so completely that the clinician does not know with what he is dealing. Without bacteriologic confirmation, not only is it more difficult to establish an adequate dosage schedule but one cannot be certain that the most effective antibiotic agent is being employed for there are instances of bacterial endocarditis in which streptomycin is the antibiotic of choice.[15,16] This consideration will assume greater importance as new antibiotic agents are introduced. The decision of when to start therapy demands careful clinical judgment. The benefits and danger of delay must be balanced one against the other. Certainly a period of delay, during which intensive bacteriologic studies are made, is advantageous provided the general condition of the patient does not contraindicate it. However, if bacteriologic confirmation is not obtained after a reasonable period of time and if sound clinical opinion arrives at a diagnosis of bacterial endocarditis, treatment should be commenced without further delay with the assurance that the majority of patients with curable endocarditis will respond to a therapeutic regimen as here outlined and the conviction that to delay is to foster the development of irreparable disease.

As a corollary to what has just been said, antibiotic therapy should not be given to patients having congenital or valvular heart disease for the treatment of a bacterial infection such as pneumonia until blood cultures have been obtained. Such individuals may have a latent bacterial endocarditis which might otherwise be obscured by the initiation of antibiotic therapy. This was brought forcibly to our attention in four individuals who developed endocarditis during an episode of pneumococcal meningitis.

During the process of healing of the bacterial lesion on the valve, rupture or fenestration of a leaflet may occur. It also seems reasonable to assume that cardiac overactivity may be a determining factor in the occurrence of embolism. Therefore, during treatment and for at least one month thereafter every effort should be made to reduce the demands on the circulation to a minimum by limiting the activity of the patient. It is of particular importance in endocarditis of the aortic valve when rupture of a partially healed cusp is observed not infrequently at postmortem.

Consideration of adequate prophylaxis against the development of subacute bacterial endocarditis is as important as the proper treatment of the established infection. Attention has often been called to the frequent occurrence of transient bacteremia following dental extraction and the consequent development of bacterial endocarditis is well recognized. Six of the patients in this series had the onset of their infections following extraction of teeth. However, not so well recognized are the potential dangers

of obstetric, gynecologic, urologic or other surgical procedures both major and minor. Two of these patients developed endocarditis after an abortion, one following manipulation of a fractured femur, one after a hemorrhoidectomy and one post partum. Hence, it seems obvious that adequate prophylaxis must be employed when any procedure, major or minor, is undertaken which might result in a transient bacteremia. Such prophylactic treatment must be given even to individuals with minimal evidence of valvular heart disease. Since the organisms producing bacterial endocarditis have a widely varying sensitivity to penicillin, it would seem wise to employ at least 500,000 units of penicillin daily as a prophylactic measure. Even this dosage may be inadequate protection against such organisms as the Streptococcus fecalis. The period of administration should be for not less than four days following the procedure.[12]

In addition to antibiotic prophylaxis, attention should be called to the importance of searching for and eliminating all foci which might serve as a reservoir of infection or reinfection. One of these patients had a recurrence several months after what seemed to be a successful course of treatment. An alpha-streptococcus was grown from her blood and also from the socket of an abscessed tooth which was extracted. She has subsequently remained well following a second course of treatment.

Because of the dual nature of subacute bacterial endocarditis, one must anticipate that a certain number of patients will develop cardiac failure, perhaps ending in death, as the result of irreparable damage to endocardium and myocardium even though cured of infection by penicillin. This damage may result either from the infection or the underlying process. In any given instance, it would obviously be difficult to estimate the degree of responsibility for cardiac impairment attributable to the bacterial endocarditis or to the underlying heart disease. There is nothing to indicate that the administration of penicillin precipitates cardiac failure in patients with subacute bacterial endocarditis through any mechanism such as rapid dissolution of bacterial vegetations before healing has progressed sufficiently. Fiese[17] has shown statistically that treatment with penicillin postpones cardiac failure and reduces significantly its incidence. Approximately 30 per cent of his series of twenty-five treated patients suffered cardiac failure as contrasted with 80 per cent in a group of forty untreated patients followed to autopsy. In our series of patients, about eight died in cardiac failure. We have studied the effect of the cardiac status prior to the onset of bacterial endocarditis upon the ultimate outcome of treatment and also upon the incidence of myocardial insufficiency occurring during the course of the disease. Two individuals with mild cardiac failure prior to the onset of their infection died during the course of treatment from apparent cardiac failure while four patients similarly affected recovered from their infection. Two of this group have remained entirely well while the other two still have evidences of mild cardiac insufficiency. These patients have been followed for periods of four, twenty-six, twenty and thirty-six months respectively. Only one patient had had severe cardiac failure prior to the development of endocarditis and he died during treatment. After the development of bacterial endocarditis seventeen of this series of patients showed evidence of varying degrees of cardiac impairment, manifested either by enlargement of the heart or signs and symptoms of obvious failure. Of these, ten had never previously manifested cardiac insufficiency prior to the development of bacterial endocarditis while six had shown a mild degree and one a severe degree of impairment. When the effect of the development of cardiac impairment after the onset of endocarditis was related to the ultimate outcome of treatment, it was found that all four of the patients who developed severe cardiac failure died while ten who had only a mild degree recovered and three similarly affected died. One-half of the group who recovered have remained apparently well

over a period of observation varying between three and thirty months while the remainder still show a mild degree of cardiac inadequacy. A single patient has shown progressive cardiac enlargement and failure three months after termination of treatment. It would thus seem that a severe degree of cardiac impairment present either before or after the development of bacterial endocarditis carries a very bad prognosis, such patients usually dying of cardiac failure despite the institution of penicillin treatment. On the other hand, patients with only a mild degree of cardiac damage incurred either before or after the onset of bacterial endocarditis generally have a successful outcome of penicillin treatment and during the period of observation have not shown a tendency to develop progressive cardiac failure, with but one exception. This latter point is a most important and encouraging observation. As was to be expected, all the individuals who had cardiac insufficiency before the development of bacterial endocarditis continued to show this disability after the onset of their infections, but cardiac inadequacy of greater or less degree frequently appeared during the course of subacute bacterial endocarditis in individuals who had not been previously so affected. The age of the patient and the type of underlying valvular disease did not seem to have any prognostic significance. There was some indication that a long interval of time between onset of symptoms and commencement of treatment was more likely to result in cardiac insufficiency than was a short interval but the difference was not statistically significant in this small group of patients.

Consequently, it becomes apparent that despite adequate penicillin treatment, failure must be anticipated in a certain number of instances. At times this will be due to cardiac failure. In others, an embolic episode may be responsible or the infection may be caused by bacteria insensitive to available antibiotic agents. The final determinants of success in the penicillin treatment of this disease are not primarily such factors as the age of the patient, the duration of the disease or the particular valves involved but rather the degree of cardiac damage resulting either from the bacterial infection or an underlying disease process, the critical nature of the embolic episodes and the resistance of the infecting organism. These are the factors which determine ultimate success or failure and it is only through the insurance of adequate penicillin treatment that they can be favorably altered.

SUMMARY

Experiences are related in the management of thirty-five patients with subacute bacterial endocarditis treated solely with penicillin on the wards of the Johns Hopkins Hospital. Attention is called to the difficulty of establishing a clinical diagnosis at an early stage of the disease due to the nonspecific or misleading character of the presenting symptoms, the frequent absence of classical physical findings and the prevalence of the infection in individuals with only a minimal degree of cardiac disease. The importance of early diagnosis and institution of treatment is emphasized, as continuation of infection may result in irreparable damage to the heart or kidneys or allow the occurrence of fatal emboli, although in several instances a successful therapeutic result was achieved despite a long lapse of time from the onset of disease until commencement of therapy. It is suggested that any patient with a cardiac murmur and a persistent fever should be suspected of having bacterial endocarditis until careful bacteriologic studies and clinical observations have proved otherwise. The necessity of retaining, both aerobically and anaerobically, all blood cultures for a period of not less than three weeks before they are considered sterile is emphasized as is the importance of searching for unusual organisms such as the genus Bacteroides. The course of these patients during treatment is described and the complications encountered are analyzed relative to adequacy or inadequacy of treatment received. The conclusion is reached that the two major causes of death were the

underlying cardiac disease and the persistence of bacterial endocarditis. Hence, the major therapeutic concern is that adequate penicillin be given for an adequate period of time and prior to the development of unalterable cardiac abnormalities. The fact that evidence of active bacterial endocarditis was found upon autopsy examination of three patients who died while receiving treatment commonly regarded as adequate has led to critical appraisal of present criteria of therapeutic adequacy. A plan of therapeutic management is described which is thought to assure adequate therapy for the maximum number of patients. In it the penicillin dosage is based primarily upon clinical evidence of satisfactory response. Such factors as the penicillin sensitivity of bacteria, penicillin blood levels and sterilization of blood cultures have been found to have only limited value. The necessity of continuing treatment for an adequate period of time is discussed and the recommendation is made that 100,000 units of penicillin given intramuscularly every two hours for eight weeks be considered the basic and minimal treatment schedule. The pros and cons of initiating treatment before a bacteriologic diagnosis is completed are stated with the conclusion that a reasonable period of delay is justified provided the condition of the patient does not contraindicate such treatment. It is advised that blood cultures be obtained before antibiotic therapy is given to any patient with valvular or congenital heart disease who has a localized bacterial infection, lest a latent bacterial endocarditis be obscured. The value of prolonged convalescence to allow maximal healing of damaged valves is indicated. Consideration is given to the need for adequate prophylaxis against the development of subacute bacterial endocarditis not only during dental extractions but during any type of procedure which might result in transient bacteremia. The elimination of foci of infection which might serve as a reservoir of infection or reinfection is recommended. In conclusion, the immediate results of treatment are discussed and the course of surviving patients over a three to thirty-six months' period is described. An evaluation is attempted of the influence upon the ultimate outcome of certain factors, including the presence of cardiac failure before, during and after the onset of bacterial endocarditis. The final determinants of failure or success in the treatment of subacute bacterial endocarditis with penicillin appear to be the degree of cardiac damage resulting either from the bacterial infection or an underlying disease process, the severity of the embolic occurrences and the resistance of the infecting organisms.

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Effect of Penicillin on the Bacteremia Following Dental Extraction*

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THE bacteremia which often follows dental extraction is believed to be of importance in the pathogenesis of subacute bacterial endocarditis. This investigation was undertaken in an attempt to evaluate the efficacy of penicillin as a prophylactic agent in preventing such bacteremia.

Horder, in 1908, was probably the first to suggest that the portal of entry for the infecting organisms in subacute bacterial endocarditis might often be the oral cavity.[1] Since then, the rôle of transient bacteremia in the pathogenesis of subacute bacterial endocarditis in patients with rheumatic or congenital heart disease has come to be generally accepted[2–9] and is based upon the following considerations: (1) the only route by which bacteria can reach the endocardium is via the blood stream; (2) transient bacteremia frequently follows dental extraction and (3) the onset of bacterial endocarditis often occurs shortly after the extraction of teeth.

It has been shown conclusively by a number of investigators[10–15] that transient bacteremia often occurs after dental extraction; indeed, bacteremia has been demonstrated after the mere chewing of gum or hard candy and following manipulation of teeth without extraction.[16–19] That bacteremia originates because bacteria at the site of extraction gain access to the blood stream has been clearly demonstrated by the ingenious experiment of Burkett and Burn who painted the gingival tissues surrounding a tooth about to be removed with a fluid culture of Serratia marcescens; the organism was recovered from blood cultures obtained shortly after extraction of teeth.[20] In Table I, experimental data bearing on these studies are summarized. In addition, it is of interest to note that transient bacteremia may follow tonsillectomy,[21–26] aural surgical operations,[27–29] manipulative procedures involving the urinary tract,[30–36] passive motion of suppurative joints and massage of furuncles.[16] Bacteremia and bacterial endocarditis have been reported also following parturition and instrumentation of the female genital tract.[37–47]

Although complete bacteriologic studies were not performed in many of the foregoing investigations, the predominating organism recovered was the alpha hemolytic streptococcus which has been shown to be the most common inhabitant of the oral cavity[48–53] and is frequently associated with apical dental infection.[52]

The temporal relationship between tooth extraction and the onset of subacute bacterial endocarditis has been noted repeatedly by many clinicians.[14,15,18,54–63]

Once the significance of the oral cavity as the portal of entry of the infecting organisms in bacterial endocarditis was recognized, attempts at prophylaxis were undertaken. Initially, methods such as cautery and curettage were suggested in an effort to prevent the escape of organisms into the blood stream[55,60,64,65] but experimental evidence of the efficacy of these methods is

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meager. Curettage has been shown to be ineffective.[12] That oral hygiene is important in decreasing the incidence of bacteremia is attested by numerous studies including the present one.[10,18,60,64]

Soon after the introduction of the sulfonamides, their use in the prophylaxis of dental bacteremia was suggested by a number of writers[14,60,66–69] and experimental studies were undertaken by several groups of investigators. In a series of twenty-seven patients with "congenital or valvular heart disease" who were given sulfapyridine before and after extraction, blood cultures taken immediately after extraction were sterile and no patient developed bacterial

TABLE 1

EXPERIMENTAL INVESTIGATIONS OF BACTEREMIA FOLLOWING DENTAL PROCEDURES

Investigator	Procedure	Dental Condition	Anesthesia	Time of Blood Cultures in Relation to Procedure	No. of Patients in Series	Positive Blood Cultures Per Cent
Richards[16] (1932)	Gum massage	Inflamed gums	None	Immediately after	17	18
				One hour after	17	0
O'Kell and Elliott[10] (1935)	Multiple extraction	Marked pyorrhea	General	Immediately after	40	75
	Multiple extraction	Moderate pyorrhea	General	Immediately after	60	70
	Single extraction	Normal	General	Immediately after	10	10
	Two or more extractions	Normal	General	Immediately after	28	43
Round, Kirkpatrick and Hails[17] (1937)	Patients chewed hard candy	Five patients with dental absorption; others not stated	None	Immediately after	10	20
Burket and Burn[20] (1937)	Extraction and application of Serratia marcescens to the gums	Not stated	Local	Immediately after	53	23
Palmer and Kempf[13] (1939)	One or two extractions	Not stated	Local	Immediately after	82	17
				Ten minutes after	82	1.7
Hopkins[11] (1939)	One or two extractions	Not stated	Not stated	Immediately after	108	16.8
				Ten minutes after	1	100
				Thirty minutes after	17	0
Elliott[18] (1939)	Rocking of tooth	Marked pyorrhea	Not stated	Not stated	21	86
		Normal	Not stated	Not stated	21	25
Murray and Moosnick[19] (1941)	Patients chewed paraffin for one-half hour	"Dental disease"	None	Immediately after	336	55
Faillo[15] (1942)	Extraction; unstated number	Not stated	Local	From immediately to six hours after	20	40

endocarditis.[70] Although in this investigation para-aminobenzoic acid was introduced into the media to inhibit sulfapyridine, the failure to include control observations makes evaluation of the results difficult. In another study[71] of ninety-seven patients who did not receive prophylactic sulfonamide therapy, positive blood cultures were obtained in twelve (12.8 per cent) following dental extraction; of seventy-three patients given sulfathiazole, positive blood cultures were obtained after dental extraction in seven (9.6 per cent). The difference in the two series is not statistically significant. It was shown that the prophylactic use of sulfanilamide led to a decrease in the number of positive blood cultures obtained ten minutes after dental extraction but no decrease occurred in the number of positive cultures obtained immediately after extraction.[12] Para-aminobenzoic acid was not used in the media in this particular study. Table II summarizes these reports. One case of fatal bacterial endocarditis, thought to have followed dental extraction performed under sulfanilamide prophylaxis, has been reported.[62]

The use of penicillin in the prophylaxis of subacute bacterial endocarditis after dental extraction has been advocated by several writers[72–75] but experimental evidence of its value has not yet appeared. The failure of penicillin to prevent bacterial endocarditis after tooth extraction has been reported twice;[76,77] in one instance,[76] relatively small doses of the antibiotic were used and in the other[77] a single injection of 400,000 units of penicillin in oil with beeswax was given prior to extraction. Three other cases of subacute bacterial endocarditis occurring despite the prophylactic use of penicillin have been observed;[78] in one of these, oral penicillin was being given to prevent streptococcal infection in a child subject to recurrent rheumatic fever.

TABLE II

EXPERIMENTAL INVESTIGATIONS OF THE EFFECT OF SULFONAMIDE PROPHYLAXIS ON DENTAL BACTEREMIA

Investigator	Procedure	Dental Condition	Anesthesia	Time of Blood Sampling in Relation to Procedure	No. of Patients in Series		Positive Blood Cultures Per Cent	
					Control Group	Sulfonamide Group	Control Group	Sulfonamide Group
Brunitz, Nizel and Berg[70] (1942)	Extraction	Not stated	Not stated	Immediately after	..	27	....	0
				Thirty minutes after	..	27	....	0
Northrup and Crowley[71] (1943)	Extraction	Not stated	Local	Immediately after	97	73	12.8	9.6
				Ten minutes after	97	73	0	0
Pressman and Bender[12] (1944)	Extraction	Normal to marked pyorrhea	Local	Immediately before	30	30	3.3	0
				Immediately after	30	30	83.3	76.7
				Ten minutes after	30	30	33.3	13.3

METHODS

Selection of Patients. The first, or control series, consisted of consecutive, unselected out-patients from either the Dental Surgery Clinic of the Washington University School of Dentistry or the Barnes Hospital Department of Dental Surgery. Subjects for the second, or penicillin, series were in-patients of the Homer G. Phillips Hospital or the Barnes Hospital group; they were seen in consultation by a dental house officer because of the finding of dental disease on physical examination. No patient in either series had received a sulfonamide drug or penicillin for at least one month prior to the observations.

Technic of Blood Cultures. In both series, blood cultures were obtained within one hour prior to extraction before any oral manipulation was done; postoperative cultures were obtained usually within two minutes and always within five minutes of extraction.

Twenty-three cc. of blood were drawn with aseptic precautions and transported immediately to the laboratory in a flask containing 3 cc. of a 4 per cent solution of sodium citrate. A flask containing 100 cc. of beef infusion broth[52] was inoculated with 10 cc. of blood and for growth under reduced oxygen tension, 10 cc. of blood were placed in a flask of thioglycollate broth.[79] The latter medium was contained in a Florence flask of 125 cc. capacity in order to decrease the area of the surface in contact with air. In addition, poured plates were made with 1 and 2 cc. amounts of blood added to beef infusion agar. The final pH of all media was 7.6.

In the penicillin series, for both pre- and postextraction cultures, a solution containing 4 units of penicillinase per cc., prepared by diluting dried commercial penicillinase with beef infusion broth, was added to the citrate flasks before the blood was introduced. That this amount of penicillinase was sufficient to cause immediate inactivation of the penicillin in the blood was determined by preliminary experiments described in a subsequent section.

Cultures were incubated at 37°C. for six days; at that time, the broths were subcultured on blood agar plates and observed for two days; if no growth had appeared, they were discarded. The poured plates were examined at frequent intervals and when colonies were seen they were described according to color and hemolysis. Colonies were then subcultured and the organisms classified morphologically according to Gram-staining characteristics; alpha hemolytic colonies were further characterized in regard to solubility in desoxycholate solution.[80] Poured plates exhibiting no growth were discarded on the sixth day.

Cultures were considered positive if organisms were recovered from either of the broths or either of the poured plates. In a few instances, organisms were recovered which were considered to be contaminants; these included diphtheroids, Staphylococcus albus and Bacillus subtilis.

Use of Penicillinase in Blood Cultures. The inactivation of penicillin, carried in the blood drawn from the patient into the culture medium, was considered essential in order that false-negative results might be avoided. Significant disadvantages inherent in the use of takadiastase, clarase and cysteine as penicillin inactivators have been described.[81–84] Penicillinase, on the other hand, is well adapted to use as an inactivator of penicillin[83, 85–88] and preliminary experiments were performed in order to determine the amount of penicillinase necessary for this purpose under the particular conditions of our blood cultures. Table III shows the results of three experiments which indicate that 4 units of penicillinase per cc. of blood drawn were adequate to inactivate larger amounts of penicillin than would usually be present in the blood with the given dosage. This amount of penicillinase also had no significant inhibiting effect on bacterial growth.

Each test was carried out as follows: The contents of a vial containing 1,000 units of dried commercial penicillinase[89] were dis-

solved in beef infusion broth and dilutions were distributed in tubes in order to give the amounts of penicillinase shown in the table. Twenty-three cc. of normal human blood were drawn with aseptic precautions and introduced into a flask containing 3 cc. of a 4 per cent sodium citrate solution. A culture of bacteria in broth was diluted with broth so that suitable numbers of bacteria, as estimated from preliminary tests, could be added to the flask. Two cc. of the resulting blood-citrate-bacteria mixture were added to each tube. Five or ten units of penicillin in 0.5 cc. of broth were added as the last step. After adjusting the volume of each tube to 3 cc. with broth and mixing thoroughly 1 cc. of each mixture was removed immediately for preparation of poured plates. Colony counts were made after incubation at 37°C. for forty-eight hours.

It may be noted in these tests that the penicillin was added last to the mixture in order to avoid any antibacterial action by the penicillin during the time taken in adding penicillinase. In the final blood cultures, the penicillinase was mixed with the citrate before the blood was drawn from the patient in order to start the inactivation of the penicillin carried over in the blood as soon as it was removed from the body. The preliminary tests showed that neither citrate nor human blood inactivated the penicillinase.

TABLE III

DETERMINATION OF THE AMOUNT OF PENICILLINASE NEEDED IN BLOOD CULTURES

Experiment Number	Test Organism	Tube Contents and Results	Tube Number											
			1	2	3	4	5	6	7	8	9	10	11	12
1	Staphylococcus albus	Penicillinase (units)	0.125	0.25	0.5	1	2	4	6	10	0	0	0	0
		Penicillin (units)	10	10	10	10	10	10	10	10	10	0	0	0
		Colony count	0	7	30	176	600	TNC*	TNC*	TNC*	0	TNC*	TNC*	TNC*
2	Alpha hemolytic streptococcus	Penicillinase (units)	0.125	0.25	0.5	1	2	4	6	10	0	0	0	0
		Penicillin (units)	5	5	5	5	5	5	5	5	5	0	0	0
		Colony count	0	0	2	52	148	183	194	173	0	181	174	186
3	Beta hemolytic streptococcus	Penicillinase (units)	0.125	0.25	0.5	1	2	4	6	10	0	0	0	0
		Penicillin (units)	5	5	5	5	5	5	5	5	5	0	0	0
		Colony count	0	0	0	1	4	9	11	9	0	10	9	9

* Too numerous to count.

Administration of Penicillin. Each of the patients in the penicillin series was given 50,000 units of penicillin intramuscularly every two hours day and night for twenty-four hours before extraction; the total dose was 600,000 units. The last injection was given approximately twenty minutes prior to extraction.

Determination of Penicillin Sensitivity. The sensitivity to penicillin of fourteen of the nineteen strains of organisms recovered in the penicillin series was determined by a modification of the method described by Rammelkamp and Maxon[90] as employed by Meads et al.[91]

Observation of Factors Influencing Incidence of Bacteremia. Information concerning factors which might influence the incidence of bacteremia, namely, gum conditions, type

TABLE IV

RESULTS OF BLOOD CULTURES FOLLOWING DENTAL EXTRACTION WITH AND WITHOUT PROPHYLACTIC PENICILLIN

Control Series*					Penicillin Series†				
Patient	Organisms‡ isolated in				Patient	Organisms‡ isolated in			
	1 cc. Pour Plate	2 cc. Pour Plate	Plain Broth	Thioglycollate Broth		1 cc. Pour Plate	2 cc. Pour Plate	Plain Broth	Thioglycollate Broth
1	....	.....	....	....	1				
2	....	5 A	A	....	2				
3	....	.....	....	....	3				
4	....	.....	A	....	4				
5	....	.....	....	A	5				
6	....	.....	....	....	6	2 NH	....	A	
7	....	.....	A	A	7	.....	4 NH	NH	NH
8	....	.....	....	....	8	.....	....	NH	
9	....	.....	....	....	9	.....	....	NH	
10	7 A	.....	A	....	10	.....	20 NH	NH	NH
11	....	7 A	A	....	11	.....	....	NH	
12	....	.....	....	....	12				
13	....	.....	....	....	13	.....	....	A	
14	....	.....	NH	....	14	A			
15	2 A	6 A	A	A	15				
16	4 A	2 A	A	A	16				
17	8 A	15 A	A	A	17				
18	....	.....	A	....	18	.....	....	NH	
19	....	3 A	A	....	19	.....	....	NH & A	
20	2 A	.....	....	....	20	.....	NH		
21	....	.....	A	....	21				
22	....	.....	A	....	22				
23	....	.....	A	....	23				
24	....	.....	....	....	24	1 NH			
25	1 A	.....	....	....	25				
26	....	2 A	A	A	26				
27	....	.....	....	....	27	.....	....	A	A
28	....	1 A	A	A	28				
29	....	1 A	A	....	29	.....	1 A	....	A
30	....	.....	....	....	30				
31	....	.....	....	....	31	32 NH			
32	....	2 A	A	A	32				
33	....	.....	....	....	33				
34	....	.....	A	....	34				
35	....	.....	A	....	35				
36	....	.....	....	....	36	.....	....	A	
37	....	1 A	A	NH	37	.....	1 A		
38	....	1 NH	....	....	38				
39	1 NH	2 A	NH	NH	39				
40	1 NH	1 A	NH	A	40				

* All pre-extraction cultures in this series were negative.

† Three pre-extraction cultures (No. 3,19,20) were positive for non-hemolytic streptococcus.

‡ A = alpha hemolytic streptococcus.
NH = non-hemolytic streptococcus.
Numbers indicate colony count.

of local anesthetic and number of teeth extracted was obtained for each patient. An arbitrary classification of gum condition was established as follows: (1) normal— no evidence of irritation, inflammation or suppuration; (2) abnormal— evidence of irritation, inflammation or suppuration. Further subdivision of abnormal gums was as follows: (1) gingitivis— irritation or inflammation without suppuration; (2) pyorrhea— definite suppuration, either mild to moderate or severe.

Determination of Statistical Significance. The statistical significance of results was determined by the calculation of chi square from a fourfold table utilizing the correction of Yates for small numbers.[92]

TABLE V

EFFECT OF PENICILLIN AND OTHER FACTORS ON THE BACTEREMIA FOLLOWING DENTAL EXTRACTION

Other Factors		Control Series			Penicillin Series		
		No. of Patients	No. of Patients with Bacteremia	Per Cent of Patients with Bacteremia	No. of Patients	No. of Patients with Bacteremia	Per Cent of Patients with Bacteremia
Total No. of Cases		40	27	67.5	40	17	42.5
Condition of gums	Normal	21	12	57.2	11	5	45.4
	Abnormal	19	15	78.9	29	12	41.4
	Gingivitis	8	6	75	13	6	46.2
	Mild to moderate pyorrhea	6	4	66.6	8	1	12.5
	Severe pyorrhea	5	5	100	8	5	62.5
Number of teeth extracted	One	16	10	62.5	26	7	26.9
	Two or more	24	17	70.8	14	10	71.4
Type of local anesthesia	Infiltration or infiltration and block	24	18	75	13	5	38.4
	Block (conduction) alone	16	9	56.3	27	12	44.4

RESULTS

Table IV presents the results of blood cultures taken immediately following dental extraction both in control patients and in those following prophylactic penicillin. It may be seen that the bacterial content of the blood was never high and that frequently the organisms were recovered from only one of the broths or plates while the other, prepared from the same blood sample, remained sterile. Nevertheless, the significance of the bacteria isolated is attested by the sterility of pre-extraction blood cultures which were made in every case. In only three instances were pre-extraction cultures positive and in two of these the cultures after removal of the teeth were positive for the same organism. Although the use of prophylactic penicillin reduced by 37 per cent the incidence of bacteremia following extraction and also reduced the number of bacteria as judged by fewer positive isolations from single specimens, it did not completely prevent bacteremia in a number of cases.

Of the twenty-seven positive blood cultures obtained in the control series, twenty-two (81.5 per cent) were due to alpha hemolytic streptococci, two (7.4 per cent) to non-hemolytic streptococci and three (11.1 per cent) to both. In contrast with these results, of the seventeen positive blood cultures in the penicillin series, only five (29.4 per cent) were due to alpha hemolytic streptococci whereas in ten (58.8 per cent) non-hemolytic streptococci were recovered; in two (11.8 per cent) both organisms were present.

The penicillin sensitivity of fourteen of the nineteen strains of organisms recovered from patients who had received the antibiotic prophylactically was determined; the results of these tests did not indicate significant penicillin resistance in any of these fourteen organisms.

In Table v the influence of various factors on the incidence of bacteremia is shown. The use of penicillin did not affect definitely the occurrence of bacteremia in patients with normal gums but in those with evidence of gingival disease there was a significant decrease in the number of positive blood cultures obtained. Examination of the results when the gum condition was more specifically classified, suggests that penicillin was particularly effective when pyorrhea existed but the results in these subgroups are not statistically significant.

Prophylactic penicillin therapy was identified with a significant decrease in the occurrence of bacteremia when only one tooth was removed; when multiple extractions were performed, bacteremia occurred with equal frequency in each series.

The use of penicillin decreased the incidence of bacteremia whether infiltration or block anesthesia was used. In the control series, positive blood cultures occurred less often after block than after infiltration anesthesia.

COMMENTS

It is apparent from the results that penicillin, while effective in reducing the incidence of bacteremia after tooth extraction, did not prevent its occurrence in a large number of patients. Furthermore, although alpha hemolytic streptococci predominated in the control series and non-hemolytic streptococci in the penicillin series, resistance to penicillin was not demonstrated in the strains of the latter group of organisms. Hence, the failure of penicillin, as used in this study, to prevent bacteremia completely cannot be attributed to resistant bacteria. The explanation for the predominance of one organism in the first series, and another in the second, is not apparent.

The data collected support the contention of other investigators[10,18] that gum disease predisposes to bacteremia after tooth extraction; under such circumstances penicillin appears to be more effective, presumably by combatting local infection.

In spite of the fact that our results in the control series do not confirm the hypothesis that multiple extractions increase the incidence of bacteremia,[2,54,55] prophylactic penicillin did decrease the number of positive blood cultures after single extractions. This result suggests that it may be desirable to extract teeth singly when penicillin prophylaxis is indicated.

The influence of the type of anesthesia employed is difficult to evaluate. General anesthesia, which obviates local trauma prior to extraction, has been advocated by several writers;[2,54,64] others have suggested that local anesthetics containing vasoconstrictors decrease the incidence of bacteremia.[20,55] No adequate study of this problem has been made and our results do not justify definitive conclusions; in the control series, incidence of bacteremia was significantly lower when conduction anesthesia was used; in the penicillin series, positive blood cultures were equally common with either form of anesthesia. It seems plausible that infiltration anesthesia, because of the trauma incident to its introduction directly at the site of extraction, contributes to the likelihood of bacteremia, especially when gum infection is present.

In a study of bacteremia following dental extractions, care must be exercised with

technical factors such as the media used, prompt inoculation and incubation of the blood cultures, prolonged observation of cultures and adequate identification of organisms. Blood cultures must be obtained almost immediately after extraction, for the number of bacteria in the blood is small (Table II) and decreases rapidly; ten minutes after extraction, positive blood cultures are uncommon.[10,13,71]

If penicillin is effective as a prophylactic agent in preventing subacute bacterial endocarditis after dental extraction, three possibilities for its mode of action may be considered: (1) complete sterilization of the gums so that bacteremia does not occur, (2) immediate destruction of the organisms in the blood stream so that implantation on the endocardium is prevented or (3) prompt destruction after implantation before clinically detectable involvement occurs. Our observations indicate that complete sterilization of the gums is not achieved with large doses of penicillin for twenty-four hours nor does immediate destruction of the organisms occur in the blood stream since bacteremia was still detected in a considerable number of cases. Nevertheless, the decreased incidence of bacteremia is not without value. Also, the failure to eliminate the bacteremia completely does not necessarily mean that penicillin will not prevent subacute bacterial endocarditis since the antibiotic agent may well inhibit the bacteria after implantation on the endocardium.

Therefore, the following principles are proposed: In patients with rheumatic or congenital heart disease who are to have dental extraction, penicillin should be given in large doses prior to operation; in the presence of gum infection, it should be given for at least twenty-four hours before operation. In all cases, it should be continued for at least two days after extraction or longer, especially if the operative site does not heal. Single extractions are to be preferred to multiple.

The hospitalization of patients for simple dental extraction is not always practical; further information concerning the efficacy of oral penicillin or of penicillin in oil and beeswax in relation to bacteremia following dental extraction would be of value.

SUMMARY

The administration of large doses of penicillin for twenty-four hours prior to dental extraction caused a significant decrease in incidence of bacteremia following extraction but failed to prevent it in a large number of cases. The agent was particularly effective in decreasing bacteremia after extraction of teeth from infected gums.

The possible *modus operandi* of prophylactic penicillin in preventing subacute bacterial endocarditis is suggested and the recommendation made that this agent be given to all patients with rheumatic and congenital heart disease before and after dental extraction.

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Sulfonamide Therapy of Subacute Bacterial Endocarditis*

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IN spite of the present availability of newer and more effective antibiotics for the treatment of subacute bacterial endocarditis, a review of experience gained during the pre-penicillin era (1938 to 1943) indicates that the sulfonamide treatment was not without merit. A follow-up study of fourteen patients who were apparently cured by sulfonamides three to eight years ago has been sufficiently rewarding to warrant this report.

ORAL THERAPY

Between 1938, when sulfanilamide was first used for the treatment of subacute bacterial endocarditis, and 1943, when sulfadiazine was replaced by penicillin, ninety-seven patients with the disease were treated with reasonably adequate amounts of one or more of the sulfonamides over a prolonged period. Eighty-one patients received oral therapy, 1.0 to 2.0 Gm. every four hours, for periods ranging from ten days to fourteen weeks.‡ In this group eight were cured—a recovery rate of 9.8 per cent. In two of the recovered patients hyperthermia was employed in addition to sulfonamide therapy.[3]

The organisms cultivated from the blood in the eight patients cured by oral medication were Streptococcus viridans (five patients), Staphylococcus aureus (one patient) and Haemophilus influenzae (two patients).

A variety of sulfonamides was employed in the eighty-one patients treated orally. Of the eight who responded favorably, one received sulfanilamide and fever therapy, one sulfapyridine, three sulfapyridine and sulfanilamide (one of the three also had fever therapy), two had sulfapyridine and sulfathiazole and one had sulfadiazine. The relative cure rate with the different drugs did not seem to be statistically significant. The patients treated with hyperthermia and sulfonamides also were not sufficiently numerous to warrant a conclusion concerning the adjuvant value of fever therapy.

It is of interest to note that there were three patients with H. influenzae endocarditis in the series and that two of these three responded favorably to oral sulfonamide therapy. One of the cured patients received sulfadiazine; the other was given sulfapyridine and fever therapy, supplemented subsequently with continuing doses of sulfanilamide.

Among the eighty-one patients who received oral therapy, there were sixty-eight whose infection was due to Streptococcus viridans; five of these sixty-eight recovered and were still alive and free of infection two to eight years after completing treatment, a recovery rate for the Streptococcus viridans patients of 7 per cent.

It is important to emphasize that in three of the eight patients cured by oral sulfonamide therapy, a Streptococcus viridans infection had been engrafted on a congenital heart lesion. In our entire series of ninety-

‡ S. S. Lichtman and W. Bierman reported the results of sulfonamide treatment in fifty-five patients with subacute bacterial endocarditis at The Mount Sinai Hospital previous to 1941. Their statistical observations are not exactly comparable with ours for the years 1938 to 1941 because we have preferred to omit those patients in whom insignificant or only casual doses were employed. For a review up to 1942 see LICHTMAN, S. S., *Ann. Int. Med.*, 19: 787–794, 1943.

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eight patients with subacute bacterial endocarditis who received sulfonamide therapy, there were five instances of congenital heart disease. The fact that three were cured of their infection by oral sulfonamide treatment indicates that bacterial endocarditis

TABLE I

NINETY-SEVEN PATIENTS WITH SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH SULFONAMIDES—1938 TO 1943

Oral therapy—1.0 to 2.0 Gm. every 4 hours for 10 days to 14 weeks		81
Causative Organisms—Streptococcus viridans	68	
Streptococcus anhemolytic	6	
Streptococcus hemolyticus β	2	
Enterococcus	1	
Staphylococcus aureus	1	
H. influenzae	3	
Recovered—follow-up 2 to 8 years		8
Streptococcus viridans	5*	
Staphylococcus aureus	1	
H. influenzae	2	
Massive Intravenous Therapy—30.0 Gm. in 3 hours		16
Causative Organisms—Streptococcus viridans	14	
Streptococcus anhemolytic	1	
Streptococcus hemolyticus β	1	
Recovered—follow-up 2 to 3½ years		6
Streptococcus viridans	6	

* This includes three recovered patients (out of a series of five) with congenital heart disease with superimposed Streptococcus viridans infection.

patients with congenital heart disease have a much better opportunity for recovery with this drug than those in whom the underlying lesion is of the acquired type. Our experience with the treatment of these patients has been so favorable that we believe ligature of a patent ductus arteriosus as performed by Touroff and Vesell[4] should be deferred until adequate treatment with sulfadiazine or penicillin has been tried.

If the five cardiacs with congenital heart disease are subtracted, our percentage of cures by oral sulfonamide in the remaining sixty-three patients with Streptococcus viridans endocarditis falls from 7 to 3.2 per cent. Apparently, the prognosis in regard to oral sulfonamide therapy of subacute bacterial endocarditis is favorable only if the infection is due to H. influenzae or other highly susceptible bacteria, or if in patients with Streptococcus viridans the infection is based on a congenital heart lesion.

MASSIVE INTRAVENOUS THERAPY

In 1942, Dick[5] reported the recovery of a patient with Streptococcus viridans endocarditis following the intravenous administration of 40.0 Gm. of sodium sulfadiazine in 500 cc. of distilled water. An acute renal injury was induced, manifested by hematuria, oliguria and azotemia. As a result of the temporary disturbance in renal function, the concentration of sulfadiazine in the blood attained high levels (89 mg. per cent free and 90 mg. per cent total sulfadiazine) and remained exceedingly high (73 to 23 mg. per cent free, 81 to 47 mg. per cent total sulfadiazine) for eight days. On the fourteenth day intravenous injections were resumed, 5.0 Gm. being administered every two or three days for four injections. The patient's temperature fell to normal within a few hours after the first massive treatment. Blood cultures on the third day and thereafter were sterile.

The massive therapy technic employed by Dick was unquestionably hazardous but by 1942 our own large experience with the prolonged oral administration of sulfonamides had convinced us that about 97 per cent of the patients with Streptococcus viridans endocarditis, who did not have a predisposing congenital heart lesion, were doomed to die under the conservative method of oral therapy. We were, therefore, persuaded to employ massive intravenous therapy on the next sixteen patients with subacute bacterial endocarditis due to this and related streptococci.

In each instance 30.0 Gm. of sodium sulfadiazine dissolved in 600 cc. or 1,000 cc. of distilled water was administered by slow, continuous intravenous drip in three hours. This was usually followed by some vomiting. Within twenty-four hours severe oliguria always occurred, the urine became turbid with red cells plus much albumin and the blood urea nitrogen increased to four or six times the normal. In two patients little or no urine was secreted on the first or second day. In six patients the urine became grossly bloody for a day or two. The same intensity of renal injury occurred in ten of the sixteen patients in whom the urine was alkalinized thoroughly before and during the period of treatment by means of bicarbonate of soda administered orally or intravenously.

Sulfadiazine crystals were observed in the urine in moderate amounts in four patients and in minimal amounts in five others. Obstruction of the ureters by sulfadiazine concretions was not encountered in any of the patients, in spite of the huge amounts given intravenously. The low incidence and mildness of crystalluria was probably due to the fact that immediate damage to the renal parenchyma was so severe that very little of the sulfadiazine escaped into the urine during the first week. This hypothesis is supported by the high sulfadiazine blood concentrations observed for seven or ten days after the massive intravenous injection.

The first two patients who received this heroic therapy recovered from the endocardial infection as well as from the renal damage and this encouraged continued trial of the procedure, despite the obvious risks. In fifteen of the sixteen patients treated in this manner the daily volume of urinary excretion returned to normal within seven to fourteen days after the initial intravenous injection of 30.0 Gm. of sodium sulfadiazine; the elevated blood urea nitrogen fell somewhat more slowly before it reached normal levels. Fixation of specific gravity of the urine and low phenolsulphonphthalein excretion rates usually persisted for many weeks or months after the blood urea nitrogen had returned to normal.

Probably in large part because of temporary impermeability of the damaged kidneys, the concentration of sulfadiazine in the blood reached a peak of 40 to 99 mg. per cent within the first twenty-four hours and usually fell slowly during the first week or ten days as renal function was spontaneously reestablished. There seemed to be a rough parallel between the degree and duration of the impairment of renal function and the height of the sulfadiazine level in the blood.

Administration of sulfadiazine was resumed as soon as the concentration in the blood had fallen below 10 mg. per cent. This occurred in various patients from the fourth to the fourteenth day after the initial massive treatment. An attempt was then made to maintain continued high blood levels, either by one or more intravenous injections of 5.0 Gm. of sodium sulfadiazine (100 cc. of 5 per cent solution) or by the oral administration of 1.0 to 2.0 Gm. of sulfadiazine every four hours "around the clock." Oral sulfadiazine therapy was usually continued in diminishing doses for several months after discharge from the hospital.

One case must be recorded as a treatment fatality. Renal function failed to improve as in the other fifteen patients and the patient died of uremia on the twenty-fourth day. By that day sufficient time had elapsed for complete healing of the tubular damage and the microscopic examination at necropsy no longer revealed the morphologic changes which must have been responsible for the renal insufficiency. A similar fatality after massive intravenous therapy with sulfadiazine was reported by Hull, Bayley and Holoubek.[6] Two other patients in their series survived but were not cured. Their fourth patient must be discounted, since he was moribund before treatment was initiated and died of the primary disease within sixteen hours.

However, the other side of the picture is impressive. In six of the series of sixteen patients treated in the above manner, blood cultures became sterile after the first massive intravenous injection, the fever and other clinical manifestations of infection subsided and a clinical and bacteriologic cure was apparently effected. All six patients have now been followed for two to three and one-half years; the blood cultures have remained sterile and fever and other clinical indications of bacterial endocarditis have not recurred. The cure rate in this series of sixteen patients treated with massive intravenous injections of sulfadiazine is, therefore, 37.5 per cent. This cure rate is in striking contrast to the results of oral therapy. None of the sixteen had congenital heart disease and none was due to H. influenzae. All previously had had rheumatic cardiovascular disease and in all sixteen instances the infecting organism was Streptococcus viridans or a closely related streptococcus. They belonged, therefore, to the most unfavorable group in which recovery

after oral therapy could be anticipated in only 3 per cent of the patients.

It is our impression that the blood stream and vegetations were sterilized by the initial intravenous injection of 30 Gm. of sodium sulfadiazine and the extremely high blood levels persisted for a week or more in consequence of renal damage and temporary renal impermeability. Although the continuation of additional intravenous or oral sulfadiazine medication for many weeks or months was probably advantageous in keeping the vegetations sterile until they were completely healed, such prolongation of treatment was not necessarily essential, except perhaps in those patients in whom the initial massive injection failed to produce a sufficiently prolonged high blood level.

CASE REPORTS

CASE I. J. F., was a female, aged fifty-seven years, with Streptococcus viridans, 2 colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine administered intravenously on the first day of treatment (1,000 cc. of 3 per cent sodium sulfadiazine in three hours) and 5.0 Gm. given intravenously on the seventeenth day. No alkalis were given.

No. of days after injection	0	1	2	3	4	5	6	8	9
Blood urea nitrogen	16				48	61	63	77	82
Blood sulfonamide (mg. per cent free)		75	68	67	70	57	64	41	41

No. of days after injection	11	15	16	17	18	19	23	29	32
Blood urea nitrogen	88	32	26	31	46	62	79	41	30
Blood sulfonamide (mg. per cent free)	24	0	0	14.5	13.3				

The result was gross hematuria present on the first and second days and oliguria of 20 cc. on the second day. There was a recurrence of oliguria on the seventeenth day following a second intravenous injection. Six blood cultures were sterile after initiation of the therapy. The patient was discharged in the seventh hospital week with a specific gravity of urine fixed at 1.010 and a phenolsulphonphthalein excretion of 40 per cent. The patient was followed for three years. She was found to be afebrile and asymptomatic. The urine was negative for albumin and microscopically; specific gravity was 1.020; the blood urea nitrogen six months after discharge was 11 mg. per cent. Repeated blood cultures during these years were negative.

CASE II. M. T., was a male, aged thirty-six years, with Streptococcus viridans, 36 colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously on the first day of treatment (1,000 cc. of 3 per cent sodium sulfadiazine in three and one-half hours). Beginning on the eighth day, 1.0 Gm. was administered intravenously every four hours for thirty-six hours, then 2.0 Gm. intravenously every four hours for forty hours followed by 2.0 Gm. orally every four hours for fifteen days, 1.5 Gm. every four hours for nine days, 1.0 Gm. every four hours for eight days and thereafter 5.0 Gm. a day (1.0 Gm. every four hours) for thirty-eight days. The patient was alkalinized.

No. of days after injection	0	1	2	3	5	8	10
Blood urea nitrogen	13	12	16	43	23	32	15
Blood sulfonamide (mg. per cent free)		67	67	40	19	14	34

No. of days after injection	12	14	18	26	35	40
Blood urea nitrogen		8	9	8	10	13
Blood sulfonamide (mg. per cent free)	23	38	32	28	24	18

There was pain in the flanks, nausea, frequent vomiting and singultus for three days after the initial injection. In the urine there was albumin, faint trace to 1 plus, many red blood cells and crystals only on the first day; rare red cells and crystals were present intermittently thereafter. There was oliguria on the first day of 300 cc. Thereafter the urinary output gradually increased to normal by the fifth day. The treatment was discontinued after two and one-half months because of back pain, hematuria and crystalluria in spite of alkalinization. The temperature was normal after the second day, except for an occasional slight rise during intravenous treatment. The first negative blood culture appeared on the fourth day. Thereafter the weekly blood cultures were sterile. The patient was discharged after the seventh week of therapy, with normal blood urea nitrogen but a specific gravity fixed at 1.016. The patient was followed for three and one-half years. He was found to be afebrile and asymptomatic. The blood cultures were sterile. There was no impairment in the urinary concentration and the phenolsulphonphthalein excretion was normal.

CASE III. D. G., was a male, aged twenty-seven years, with Streptococcus viridans, 21

colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously on the first day of treatment (1,000 cc. of 3 per cent sodium sulfadiazine in three hours); 1.0 Gm. administered intravenously every four hours from the fourth to the thirteenth day. Thereafter 1.5 Gm. was given orally every four hours for five days, 2.0 Gm. orally every four hours for twelve days and 1.0 Gm. orally every four hours for ten days.

No. of days after injection	1	2	3	5	8	10	16	20	27	36
Blood urea nitrogen	11	20	23	15	22	18		15		15
Blood sulfonamide (mg. per cent free)	30	24	18	20	15	48	5	9	8	5

The result was gross hematuria present on the first day, then microscopic for seven days. Moderate oliguria was present only on the first day; thereafter the output of urine was normal. The patient had severe abdominal pain and vomiting the first four days. Many crystals were present in the urine on the seventh day, and it was acid despite alkaline therapy. Fixation of specific gravity below 1.010 was persistent; on discharge the value was 1.012. The temperature fell to normal on the second day, then there was a moderate fever for three days ascribed to phlebitis. After this the temperature was normal continuously. The blood culture was negative on the ninth day. Thereafter repeated blood cultures were sterile. The patient was followed for three years. He was found to be afebrile and asymptomatic, except that he has recently begun to suffer from paroxysmal nocturnal dyspnea. The blood cultures have been sterile and the urine negative, with normal concentrations.

CASE IV. M. S., was a male, aged thirty-four years, with Streptococcus viridans, 24 colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously (600 cc. of 5 per cent sodium sulfadiazine in three hours). Thereafter 2.0 Gm. was given orally every four hours for twenty-eight days, 1.5 Gm. every four hours for four days, 1.0 Gm. every four hours for ten days, and 1.0 Gm. twice a day for forty-five days. No alkalis were given.

No. of days after injection	1	2	3	4	5	8	10	13	21	34	39
Blood urea nitrogen		31	39	55	61	41	33	22	12	16	11
Blood sulfonamide (mg. per cent free)	65	41	42	29	44.5	44	31	22	21	19	10.5

The result was gross hematuria present on the second day; later, only occasional red cells were seen in the urine microscopically. There was no decrease in the output of urine. The specific gravity was fixed below 1.010 for fifteen days, then it was below 1.018 until the patient's discharge. Moderate numbers of sulfa crystals appeared in the urine only on the second day. The temperature was normal after the twelfth day. The blood culture was negative on the eighth day. Thereafter repeated blood cultures were sterile. The patient was followed for two and one-half years. He was found to be afebrile and asymptomatic; the blood cultures were sterile and the urine was negative.

CASE V. S. Z., was a female, aged thirty-three years, with Streptococcus viridans, innumerable colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously (600 cc. of 5 per cent sodium sulfadiazine in three hours). Four days later 1.0 Gm. was given orally every four hours for ten days, 2.0 Gm. orally every four hours for seventy days and 1.0 Gm. every four hours for five months. The patient was alkalinized.

No. of days after injection	0	1	2	3	9	11	13	24	30
Blood urea nitrogen	12	39	25	30	22	15	18	10	5
Blood sulfonamide (mg. per cent free)		86	40	36	22	14	6.5	29	19

The result was that the patient tolerated the massive dose well; only mild nausea and vomiting occurred. There was no oliguria. The volume of urine was between 1,5000 and 2,000 cc. daily. The urine was usually alkaline; no sulfa crystals were present. There was no fever after the second day. The blood cultures were repeatedly sterile after the fifth day. One embolic lesion (finger) appeared ten days after the massive initial dose. Specific gravity of the urine was 1.022. The patient was discharged after eight weeks of treatment and was followed for two and one-half years. Ten days after discharge she was readmitted because of virus pneumonia from which she convalesced uneventfully. During this period of hospitalization the blood cultures were negative and the blood sulfonamide level varied between 17 and 22 mg. per cent. The patient is completely well two and one-half years later. The blood cultures have been sterile and the

urine negative. No signs of reinfection have been seen.

CASE VI. H. H., was a male, aged thirty-one years, with Streptococcus viridans, 3 colonies per cc. blood. The therapy consisted of 30.0 Gm. sodium sulfadiazine given intravenously (600 cc. of 5 per cent sodium sulfadiazine in three hours). On the fifth day he received 2.0 Gm. intravenously and on the sixth day 2.0 Gm. intravenously twice a day. After the ninth day he took 2.0 Gm. orally every four hours and 2.0 Gm. of sodium bicarbonate three times a day for two weeks; thereafter 1.5 Gm. orally every four hours for three weeks, 1.0 Gm. orally every six hours for two months and 0.5 Gm. every six hours for five months.

No. of days after injection	1	2	3	4	6	7	8
Blood urea nitrogen	13	14	52	54	70	76	85
Blood sulfonamide (mg. per cent free)	43	38	50	42	28	28	11

No. of days after injection	12	13	14	15	16	22	26
Blood urea nitrogen	31	54	49	34	25	14	13
Blood sulfonamide (mg. per cent free)	12.5	18	20	19	21	15	11.6

Before admission to the hospital this patient had received small doses of sulfadiazine (1.0 to 4.0 Gm. daily) by mouth for two and one-half months without any influence on the disease. Blood cultures after admission were repeatedly positive, 2 to 4 colonies per cc. After massive therapy he had nausea and vomiting, oliguria, albuminuria and microscopic hematuria. During the first twenty-four hours the urine output declined to 29 cc.; no urine was passed on the second day; on the third day the urine output was 300 cc. and on the fourth day it was again normal (2,000 cc.). The specific gravity of the urine continued to be fixed up to the time of discharge. A week after massive therapy only a few red cells were seen in the urine microscopically and only a few sulfa crystals and casts. The temperature became normal on the seventh day. He was discharged in the fifth week of treatment with a normal temperature, normal sedimentation rate and apparently well, except for a fixation of the urinary specific gravity. Repeated blood cultures after the seventh day following massive intravenous treatment were all sterile. The patient was followed for two and one-half years. He has been afebrile and asymptomatic; there have been no signs of infection and the blood cultures have been sterile and the urine negative.

CONCLUSIONS

1. In the pre-penicillin era (before 1943), oral sulfonamide therapy of patients with subacute bacterial endocarditis, administered in the manner described, resulted in the cure of eight of eighty-one patients, or an overall cure rate of 9.8 per cent. If patients with H. influenzae endocarditis and those with congenital heart disease are excluded, the percentage of cures with a three to eight year follow up is reduced to 3.2 per cent.

2. Two of three patients with H. influenzae endocarditis were cured by oral sulfonamide therapy. This demonstrates the value of sulfonamides as an alternative to streptomycin in H. influenzae infections.

3. Three of five patients with congenital heart disease were cured of Streptococcus viridans endocarditis by oral sulfonamide therapy without ligation of the ductus arteriosus.

4. In addition to the patients with H. influenzae and congenital heart disease, three other patients with subacute bacterial endocarditis were cured by oral therapy; in two, the infecting organism was Streptococcus viridans and in the third it was Staphylococcus aureus.

5. Massive intravenous sodium sulfadiazine therapy resulted in the cure of six of sixteen patients with subacute bacterial endocarditis caused by Streptococcus viridans. Patients with congenital heart disease were excluded from this series. The six patients have been followed clinically and bacteriologically for two to three and one-half years. The cure rate after massive intravenous therapy is, therefore, 37.5 per cent.

6. Massive intravenous sodium sulfadiazine therapy is attended by a high treatment fatality risk (over 6 per cent). In view of the risk, its use is warranted only in those patients with subacute bacterial endocarditis caused by strains of Streptococcus viri-

dans which prove to be resistant to penicillin and streptomycin.

7. In patients with congenital heart disease (not patent ductus arteriosus) and superimposed infection with an organism resistant to penicillin and streptomycin, oral sulfonamide therapy should be employed first; massive intravenous therapy is warranted only after adequate oral therapy has been attempted.

8. If the congenital lesion is a patent ductus arteriosus, ligation is an alternative primary method of therapy; if tying off the ductus is deferred and oral sulfonamide therapy proves successful, the ductus should nevertheless be ligated after recovery from the infection.

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Use of Radioactive Sodium As a Guide to the Efficacy of Drugs Used in Treatment of Diseases of the Peripheral Vascular System*

Preliminary Report

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OBJECTIVES sought in the treatment of peripheral vascular diseases are the reopening of completely or partially closed blood vessels and the development of an adequate circulation. The vasodilator drugs, papaverine hydrochloride and histamine, have frequently been reported useful in obtaining such results. These drugs may produce transient or prolonged effects. The blanched skin may become flushed and its surface temperature increased. However, at times the same dose seems to be ineffective because there are no such physical changes. Another form of therapy, used especially in thrombo-angiitis obliterans, is the intravenous administration of hypertonic (5 per cent) solution of sodium chloride. This is thought to produce a transitory hydremia. The basis for its usage is essentially empirical. There is no visual or otherwise apparent effect. If one could be assured of pharmacological activity or clinical improvement from these measures, their continued use in chronic peripheral vascular diseases could be undertaken with greater confidence.

Increasing the diameter of a capillary causes an increase in the permeability of its endothelium[8,9] while a decrease in the diameter reduces the permeability.[6,8,12] Therefore, with dilatation of the capillary, crystalloids and fluid should move more rapidly into the pericapillary space.[8–10] Rate and direction of movement of fluid are dependent upon the relationship between the blood pressure of the capillary, the osmotic pressure of the blood in the capillary and the degree of permeability of the capillary wall.[7–10] The crystalloids pass through the pericapillary space at a rate specific for each ion to reach an equilibrium on both sides of the semipermeable endothelium according to the Gibbs-Donan formula.[5]

One of the profound disturbances in obliterative diseases lies in the inability of the capillaries to take care of the nutrition of the tissues they permeate. An increase in the rate of transport across the endothelium of such capillaries would mean increased nutrition of the tissues thus supplied. It is therefore reasonable to assume that any method, to be of value in the treatment of peripheral vascular disease, should increase diffusion through the semipermeable membranes of the capillary in addition to enhancing the supply of blood. Such changes in the blood supply or the rate of diffusion can be measured with the aid of the radioactive isotope of sodium according

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to the method of Smith and Quimby.[15] They introduce this material into the circulation by intravenous injection and with a Geiger counter note its accumulation in the extravascular fluid in an extremity. This accumulation is dependent upon the patency of the minute vessels, the vascularity of the area and the permeability of the capillary endothelium. An acceleration in rate should therefore be indicative of dilatation of the minute vessels and an increase in available semipermeable membrane.

Davson and Danielli,[5] in their monograph on the permeability of natural membranes, stated that the use of radioactive isotopes should provide an accurate and rapid method for studying permeability. In accordance with their ideas change in the rate of diffusion of radioactive sodium should be dependable as an indicator of comparable variation in the caliber and permeability of the minute vessel system of the extremities and should also afford a valuable method for the study of the peripheral circulation. Experience with the venous occlusion plethysmograph, skin temperature thermocouples, oscillometer and capillary microscope has shown that they are of great help in studying the peripheral circulation but that they have definite limitations. The greatest difficulty lies in actually getting close to the blood vessels in man. By the use of radioactive sodium and the Geiger counter the course of events in vessels below the surface of the skin can be followed.

Accordingly, it seems worth while to use this type of investigation as a means of studying the effects of drugs used in treatment of peripheral vascular disease. The radioactive material in a few cc. of normal saline is injected into an antecubital vein and its arrival and accumulation in the feet is observed by the continuous recording of the Geiger counter. The injected material is well mixed with the blood in the heart. As the arteries bring the radioactive substance to the feet and it passes through the capillaries, the sodium diffuses into the extravascular fluid until equilibrium is reached. The Geiger counter registers a steady increase up to this point; the values recorded minute-by-minute can be plotted as a "sodium build-up curve." The shape of this curve depends upon the condition of the main and collateral vessels supplying blood to the feet as well as on the rate of diffusion through the capillary walls. For any individual the curve remains essentially the same on successive tests unless something has been done to affect one of these two factors. Such a test performed immediately after the application of one of the drugs under consideration might be expected to show whether it produced a vasodilating effect.

In a group of patients undergoing treatment, before any drugs were given, a basic radiosodium test was made. Various drugs were then used and the test repeated. Typical results are shown in Figures 1 to 5. Experimental points are indicated for each minute of counting, open symbols represent counts for the left foot and solid symbols represent counts for the right foot. Each chart also shows the "normal range," the region in which the curves fall for normal individuals with no vascular involvement. In some cases several drugs were tested on the same individual.

HISTAMINE

By Iontophoresis. Histamine was introduced into the skin of one foot and ankle of each of the patients tested by means of galvanic iontophoresis; the untreated foot served as a control. The histamine-containing ointment "Imadyl" was rubbed into the skin and covered with the negative electrode moistened with normal saline solution. A galvanic current 10 to 20 ma. which without histamine gives no reaction

was administered until the skin reddened or for approximately ten minutes if there was no reaction.

The patient, M. B., Unit No. 646,075 (Fig. 1), with a diagnosis of scleroderma, had a basic curve well below the normal

By Intravenous Injection. In view of this definite response from iontophoresis it seemed desirable to try other routes for the introduction of histamine. The insensitive skin of scleroderma increases the liability to an electric burn. The atrophic and broken

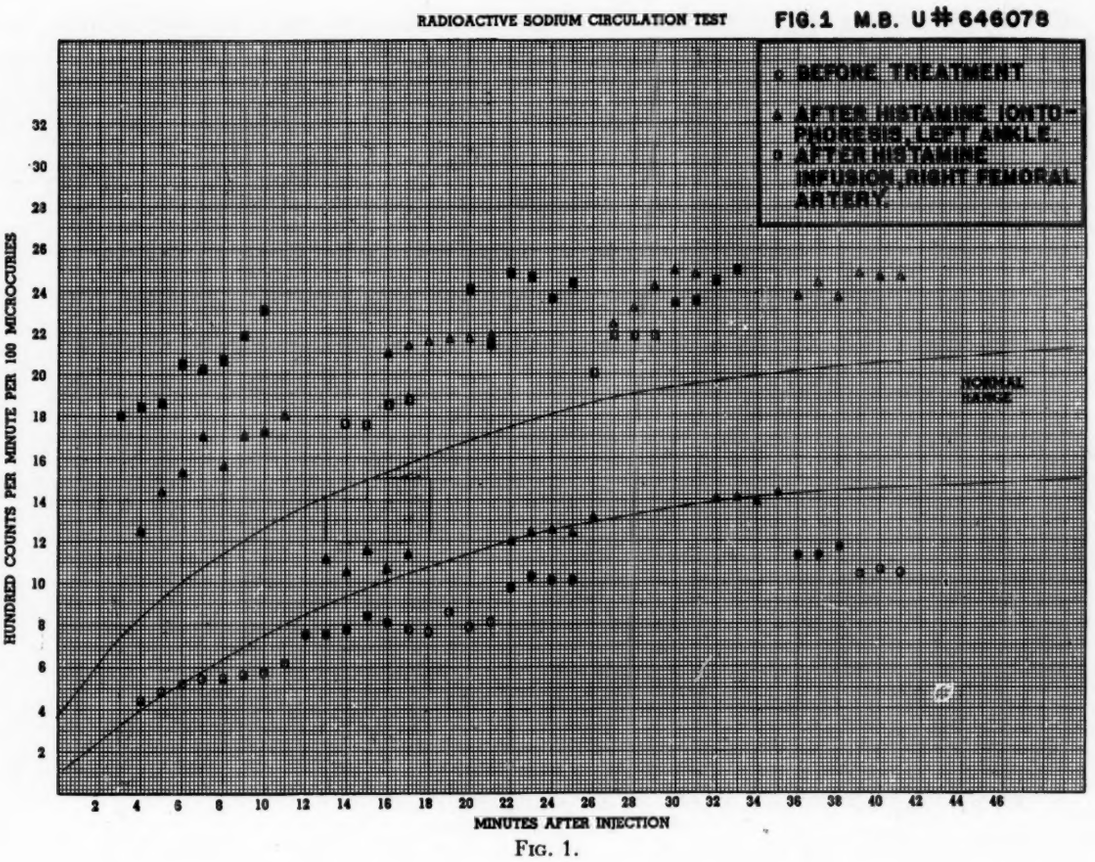

FIG. 1.

range as shown by the circles. When histamine iontophoresis was completed on her left ankle, the curve for that foot rose well above normal (triangles), while that on the untreated side remained essentially the same as before. The treated skin showed marked rubor and there was a burning sensation. This test was later repeated on the other ankle of the patient with a corresponding rise in that foot. In another case of Raynaud's disease, with the basic curve essentially normal, the rise was definite although not so marked. This patient had a dry, rigid skin which showed little reaction.

skin which is frequently present in arteriosclerotic obliterative arteritis is so sensitive that it often precludes the use of a galvanic current and Imadyl ointment. Histamine has been given intravenously to patients with multiple sclerosis without deleterious effect on blood pressure or pulse.[3] Accordingly it was tested in this series. The patient, J. I., Unit No. 448,782, with a diagnosis of thrombo-angiitis obliterans, was given intravenously 1,000 cc. of normal saline containing 2.75 mg. histamine acid phosphate (equivalent to 1 mg. histamine base) at a rate of 140 drops per minute. He quickly

felt a generalized warmth which, however, did not extend to his lower extremities. His face flushed and he complained of headache but there was no color change in his legs or feet. His basic curve (circles, Fig. 2) was in the normal range. The curve following intravenous histamine (triangles) was much lower. This test was not repeated on another patient because it was believed that in such a procedure a drop rather than a rise was the logical result and it would be of no therapeutic value.

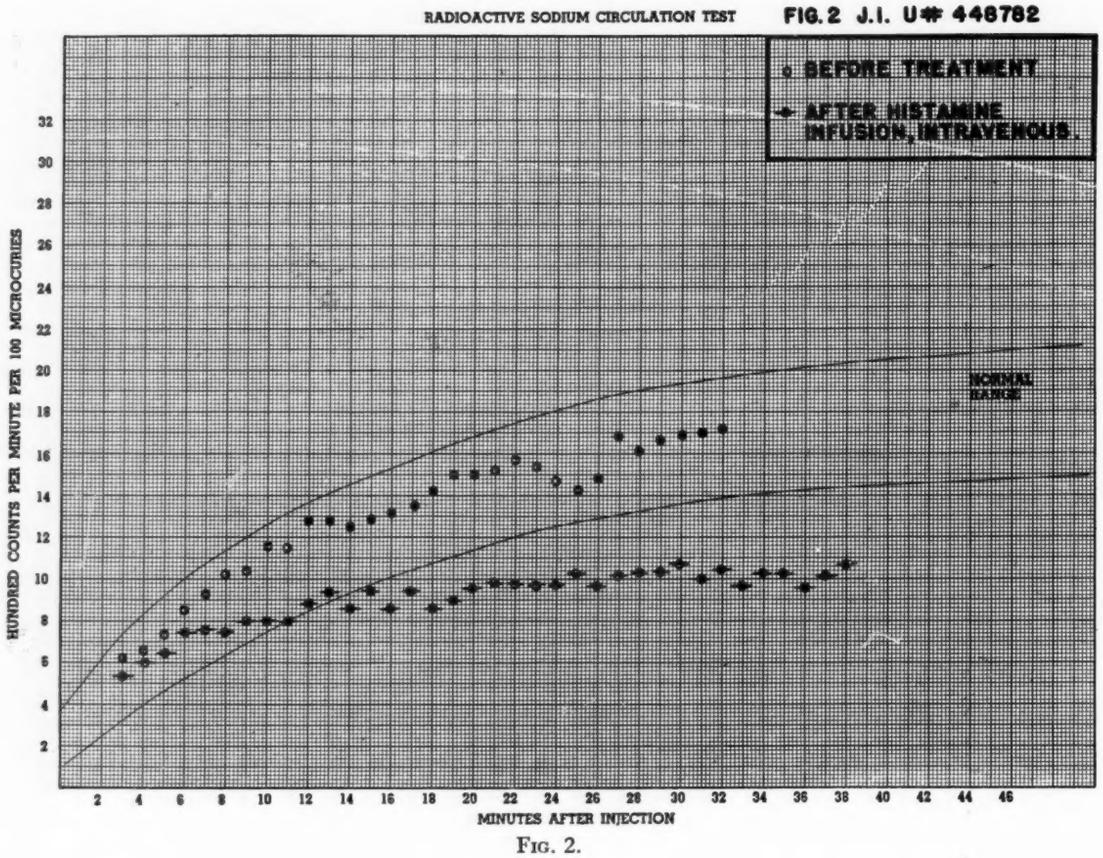

FIG. 2.

By Intra-arterial Injection. Since local administration of the drug by iontophoresis had produced an effect, it seemed that a more direct placement of the histamine might be more successful than the intravenous route. Accordingly, 0.55 mg. histamine acid phosphate (equivalent to 0.2 mg. histamine base) dissolved in 1 cc. of water was injected into the popliteal artery of patient A. B., Unit No. 708,276, who had scleroderma and had shown only moderate response to iontophoresis. The foot immediately became pink, warm and moist. The sodium curve (triangles, Fig. 3) rose sharply from the beginning and was definitely higher than the basic curve (circles) for both feet.

It was believed that perhaps a prolonged and milder effect would be more advantageous than a sharp and fleeting one. Accordingly, a drop-by-drop infusion into the femoral artery was used. The histamine was diluted in the same way as when it was administered intravenously, 2.75 mg. histamine acid phosphate in 1,000 cc. of normal saline solution (equivalent to 1 mg. histamine base). This gave a solution with a pH of 6.5. To overcome the pressure in the femoral artery, it was necessary to introduce the solution at a pressure at least

higher than the diastolic pressure in the artery. The ordinary 500 cc. infusion burette was capped by a stopper with two holes which was held down tightly with several strips of adhesive tape. Through one opening in the stopper a piece of glass tubing was inserted reaching above the histamine solution. The outer end of the tube was connected to two parts of the ordinary blood pressure apparatus by means of a Y tube. With the arm cuff rolled up snugly and held so with stout rubber bands its rubber tubing was connected to one arm of the Y tube, the tubing of the manometer to the other. A closed circuit was thus established and when the bulb was inflated a positive pressure was created in the infusion bottle which could be measured by the mercury manometer of the blood pressure apparatus.

With the skin and subcutaneous tissue anesthetized by procaine, a 2 inch, 18-gauge, short beveled needle was introduced into the femoral artery. The bright red blood and the pulsating thrust into the syringe attached to the needle were evidence of entry into the artery. The syringe was detached and the needle was connected with the flask which already had a positive pressure of at least 70 mm. Hg. The pressure was then raised or lowered until the pulsating blood could be seen in the glass-connecting tip during each systole of the heart. Inflow takes place during diastole at the rate of 90 to 120 drops per minute.

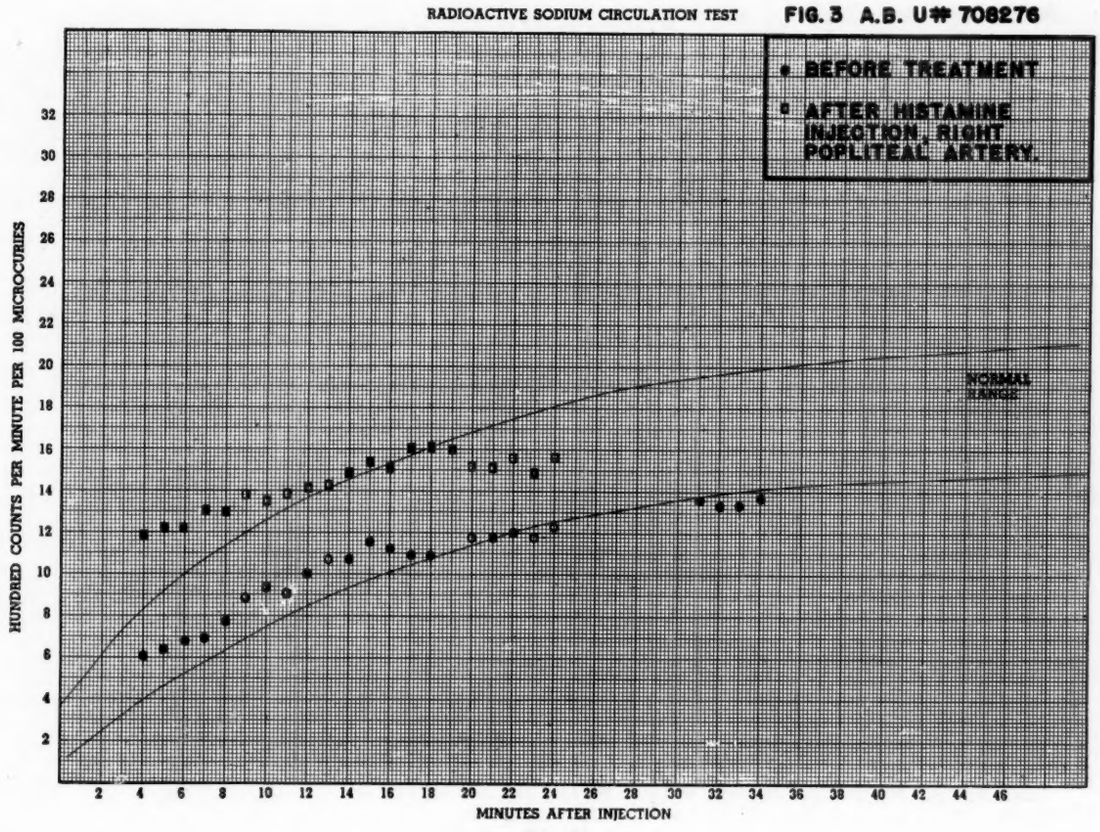

FIG. 3.

The result of such a test in a patient who had responded sharply to iontophoresis is shown by the squares in Figure 1. She received 1.37 mg. histamine acid phosphate in 500 cc. normal saline into her right femoral artery. There was prompt warming and flushing of the skin from toes to buttocks

with slight whealing but without itching. The radiosodium injection was administered as soon as the histamine started to flow. The curve shows a marked immediate rise in the right foot with both feet finally giving values much higher than in the

Several other patients have shown a similar rise in the radiosodium curve and a similar subjective response, varying in degree with the extent of the obliterative process in the larger vessels. On the other hand, in one patient, J. C., Unit No.

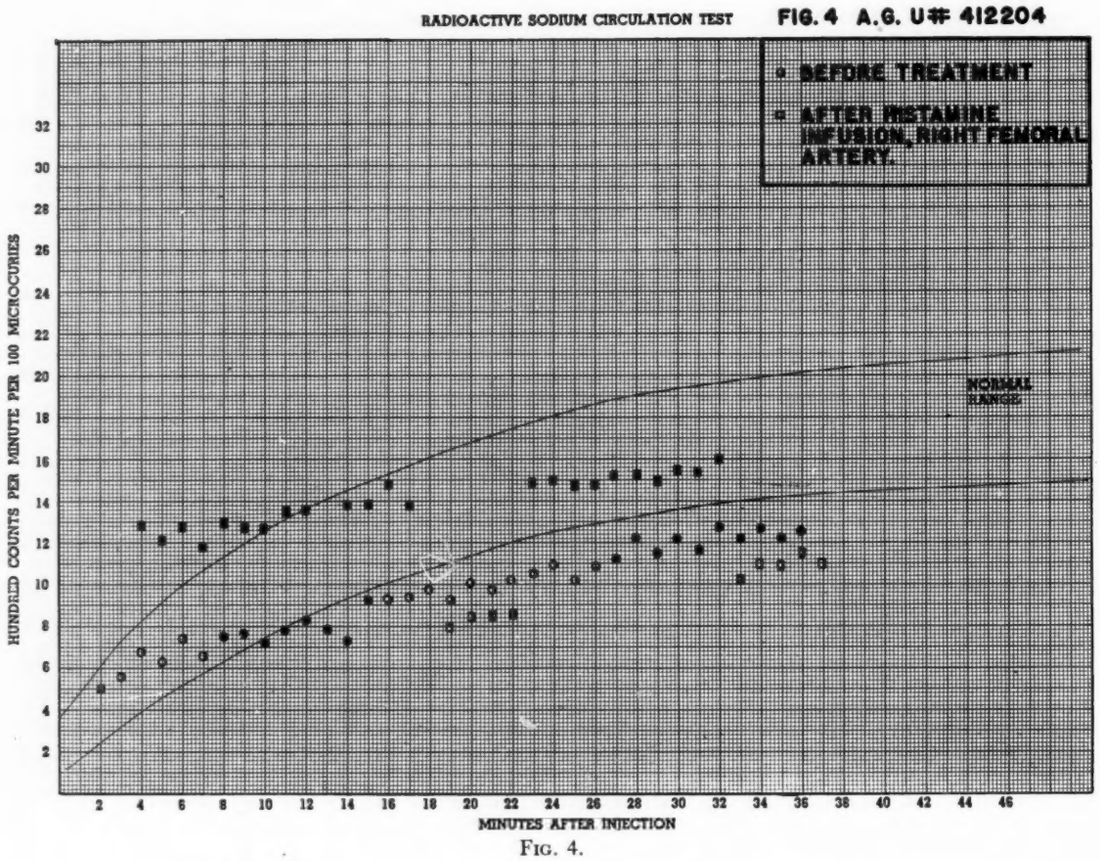

FIG. 4.

basic chart. Figure 4 shows results of the test in patient A. G., Unit No. 412,204, with dermatomyositis and Raynaud's disease. The basic curve was slightly below normal. The curve made during the infusion into the right femoral artery of 300 cc. of normal saline containing 0.3 mg. histamine base shows the right foot brought up into the normal range. The left foot remained at a low range. The skin temperature rose, the muscle temperature fell and the patient noted that this was followed by relaxation of the spastic calf and thigh muscles on the side of the infusion. This relaxation continued for several days.

731,915, with peripheral arteriosclerosis, the curve following this type of histamine treatment coincided with the basic curve.

An attempt was made to reverse the dilatation induced by histamine iontophoresis by the introduction of adrenalin intravenously. It has been shown that adrenalin injected into the skin reduces diffusion from the local blood vessels.[6] A very dilute solution of adrenalin given intravenously to patients with erythromelalgia relieves a group of characteristic signs and symptons.[11] Case M. B. (Fig. 1) showed a similar group of symptoms following histamine iontophoresis, namely, increase in skin

temperature, marked rubor and a persistent burning sensation. To study the effect of adrenalin on vessels which had been dilated in this manner, she was on two occasions given a venoclysis of 1:250,000 solution of adrenalin hydrochloride immediately following the iontophoresis. The first introduction was administered before the radioactive sodium was given and the second was given twenty-five minutes after the radioactive sodium was injected. In neither case was any effect produced on the graph of either the histamine treated foot or the untreated foot. The curves agree with those for histamine iontophoresis alone, showing no immediate reaction to the drug. There was also no alleviation of the burning sensation.

PAPAVERINE HYDROCHLORIDE

This drug has frequently been used to produce vasodilatation. In these tests 60 mg. were dissolved in 200 cc. of normal saline; 100 cc. was run into an antecubital vein in fifteen minutes. Radioactive sodium was then injected and the remainder of the papaverine allowed to run in at the rate of 25 drops per minute while the sodium curve was being taken. It was believed that in this way a potent and sustained effect of the drug would be obtained. The patient suffered no untoward effects and there were no visual changes in the skin. In four patients thus tested the sodium curves showed no change from the basic curves. One attempt (on M. B.) to alter the curve by a single dose of 0.06 mg. papaverine hydrochloride intravenously also failed to show any effect.

SODIUM CHLORIDE

Intravenous administration of 300 to 500 cc. of 5 per cent solution of sodium chloride is frequently used in patients suffering from peripheral vascular disease. Subjectively, it appears to offer some relief in a number of cases. In five patients receiving the radioactive sodium test during or immediately following the therapeutic saline injection, no change whatever was observed from the basic curve previously obtained.

COMMENTS

Although the data herein presented are based on a small series of tests, it is believed that they are sufficiently consistent to be informative. Of the substances tested only histamine caused a consistent and marked increase in the rate of diffusion and therefore vasodilatation of the minute blood vessels. The most efficient routes for the introduction of histamine in these tests were found to be through the skin by iontophoresis and intra-arterially. Primary fixation of the histamine in the wall of the blood vessels of the affected extremity, with little or no dissipation into the body, is the result desired. Allen and Crisler[2] reported that papaverine, mecholyl and histamine could not be fixed by intra-arterial injection. Their graphs for histamine are not convincing. They gave a single rapid injection of the drug and measured skin temperatures. If there was a response, the change in skin temperature would be too transient to register dilatation. Studies of radiosodium curves show that introduction of histamine by iontophoresis causes a marked increase in the diffusion of radioactive sodium. To avoid injury to atrophic, gangrenous or ulcerated skin and with the hope of reaching vessels deeper than those in the subcutaneous layer, the intra-arterial method of administering a dilute solution of histamine was devised. Administered slowly the histamine will be fixed in the tissues and destroyed by the histaminase present. When this method is used, radiosodium graphs following this procedure are definitely above the basic curves for the same individual. It is easy to follow the spreading flush of the skin of the legs and the increase in skin temperature objectively. There is also subjective improvement; the patients

quickly note a sensation of warmth which they have not experienced previously. When the intra-arterial infusion is given at a rate of 70 to 120 drops per minute in patients with marked obstruction of the larger arteries and more slowly to those with moderate obstruction, most of the drug is destroyed by the local histaminase. The optimum amount appears to be 0.7 mg. of histamine acid phosphate dissolved in 250 cc. of normal saline. To date this amount has been given in about ninety treatments with marked objective vasodilatation of the lower extremities and subjective improvement and, with one exception, without accident.

With extensive obliterative disease in the large arteries, up to 500 cc. of similar concentration can be used without danger. If the rate of injection is too rapid, flushing of the face gives forewarning of the escape of histamine into the venous circulation. To disregard this warning may cause an untoward experience, as occurred with one patient in this series. The injection was begun satisfactorily but as it later appeared the rate of the infusion was not carefully controlled. The patient's face was markedly flushed and his head had been throbbing for one-half hour when abdominal pain, diarrhea and vomiting suddenly began. His hematocrit showed hemoconcentration. These cleared after a stormy twelve hours following several saline infusions. The sodium build-up curve during the experience remained essentially the same as the basic one. It is not evident why the early part of the curve was not elevated since the pain did not begin at once.

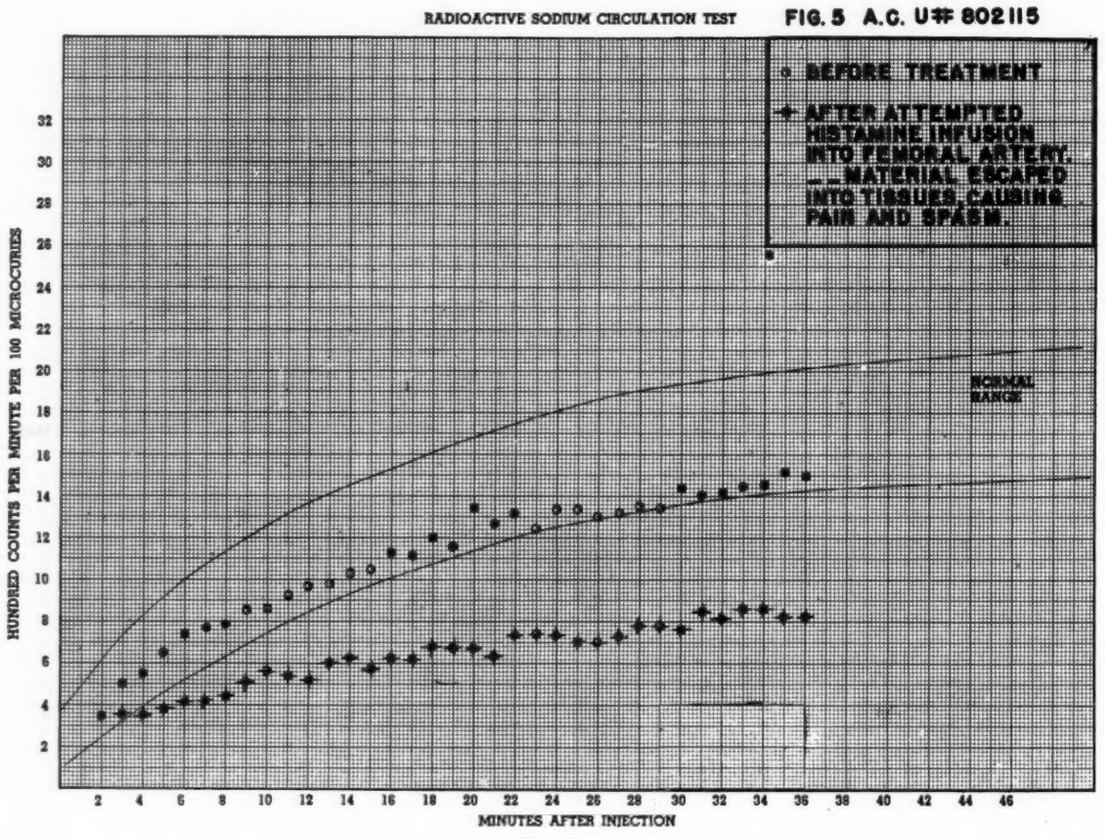

FIG. 5.

The sensitivity of the vasomotor system to pain may be an important factor in investigations of the type herein discussed. Pain may give rise to unexpected effects which must not be overlooked. This is well

illustrated by the experience with patient A.C., Unit No. 802,115, with a diagnosis of early thrombo-angiitis obliterans in whom the histamine solution failed to enter the femoral artery as intended and infiltrated the subcutaneous tissue instead. Severe pain was felt in the groin and the radiosodium curve was definitely lower than the basic curve instead of higher as was expected after the intra-arterial infusion. (Fig. 5.) This was undoubtedly the result of a reflex spasm set up by the prolonged pain caused by the misplaced drug, and is analogous to the acute capillary spasm which can be observed through the capillary microscope when the arm is pinched or when a blood pressure cuff on the other arm is inflated until pain is caused.

Intravenous histamine not only did not cause an increase in diffusion but induced a lowering of the curve in the one patient tested. The failure to raise the curve can be explained by contrasting the differences in the concentration of the drug, which is greater on direct arterial introduction and less when first diluted by the venous blood before it can reach the arterioles. When the concentration of the drug is low the most sensitive vessels will react first. It is well known that the arterial tree of the lower extremities is least sensitive and that of the head most liable to vasodilatation. The habitual erect posture has been offered as an explanation of this phenomenon. Recent studies[14] on spinal anesthesia may explain the low diffusion curve in the one patient studied. The authors showed that, as expected, a dilatation of the blood vessels in the lower extremities followed the anesthesia. However, vasoconstriction of the blood vessels of the upper extremities took place at the same time. If this compensatory mechanism does not occur, the patient develops signs of shock. The patient receiving histamine intravenously developed dilatation of the blood vessels of the upper half of his body; his head ached, his face was flushed and his arms felt warm. The drop in diffusion at the feet indicates that the compensating mechanism was effective in his case, as it was in the patients who had a low spinal anesthesia except that the effects in upper and lower extremities were reversed. Furthermore, a similar response has been found by Cook and Sears to occur in dogs after intravenous injection of histamine when radioactive krypton is utilized as an indicator.[4] They found that the peripheral blood flow in the hind paws fell while coronary circulation showed a marked increase in blood content. In view of these findings, it did not seem desirable to subject more patients to this test since larger doses of histamine theoretically would have been necessary to dilate the blood vessels of the lower extremities and such a dosage was considered too great a risk.

Papaverine administered intravenously, in spite of its stated ability to cause vasodilatation and decrease circulation time, was apparently unable to induce a measurable change in the permeability of the minute vessels of the lower extremities, at least in a single treatment. It might be effective perhaps with lesser involvement of the minute vessels but in the patients in this series, papaverine failed when histamine succeeded. When papaverine is given intravenously, with generalized dilatation of the vascular system, the usual gradient of pressure is maintained although the blood pressure may be lower. In contrast, if the dilatation is localized and a high central pressure is maintained, a higher gradient or differential will be brought about; more blood will be driven into the extremity in this manner. This is the situation when histamine is given intra-arterially.

The reduction in concentration of serum proteins which is known to follow the infusion of 300 to 500 cc. of 5 per cent sodium chloride solution is indicative of hydration of the blood. If this were of sufficient mag-

nitude, it should result in distention of blood vessels with increased capillary permeability. No evidence of this has been found in these tests and it appears that the volume increase is not sufficient. Any benefit from this treatment which is used frequently in thrombo-angiitis obliterans is certainly not the result of an immediate vascular dilatation of sufficient magnitude to be demonstrated by this method.

There are many other factors to be considered in analyzing the mechanism by which vasodilators can alter the permeability of the capillaries. In this study a radioactive sodium isotope was used and so values are established for sodium. It does not follow that other ions or the more complex organic compounds will be affected in the same way. Changes in permeability may be wholly dependent upon variations in action potential and membrane conductance induced, limited or destroyed by enzymatic processes initiated or altered by the drugs used.[5] From this point of view much work remains to be done.

CONCLUSIONS

1. Patients with scleroderma, thrombo-angiitis obliterans, obliterative arteriosclerotic endarteritis and non-specific arteritis of the minute vessels frequently show a subnormal curve for the diffusion of radioactive sodium from the blood vessels.

2. Histamine administered by iontophoresis or by intra-arterial injection brought about a definite rise in the diffusion curve. When given intravenously in one patient it produced the opposite effect.

3. The dilatation caused by histamine was not reversed by 1:250,000 adrenalin given intravenously.

4. Neither papaverine nor 5 per cent sodium chloride solution given intravenously produced changes in the radioactive sodium curves.

5. Of the drugs tested, only histamine appeared able to produce an immediate increase in capillary diffusion rate as determined by a radiosodium curve taken following a single dose.

6. A method for giving an intra-arterial infusion is described. To date ninety such infusions have been administered.

The authors wish to acknowledge their indebtedness to Miss Charlotte Schmidt for her technical assistance.

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Hypertensive Vascular Disease*

Duration of Life in a Selected Series

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IT is a well recognized statistical fact that hypertensive vascular disease and its sequelae have a detrimental effect on life expectancy. It is also generally accepted that the disease varies greatly in its intensity and rate of progression, with gradations from a benign, asymptomatic form to patients with so-called malignant hypertension with a rapidly fatal outcome. In spite of this knowledge there is a tendency to overlook the fact that a considerable number of patients carry on far better than might be anticipated on the basis of initial observations.

Many attempts have been made to record the course and prognosis of essential hypertension. Keith, Wagener and Barker, whose observations are often used as criteria to compare the results of surgery with medical management, describe four types of hypertensive vascular disease based chiefly on the degree of retinitis.[1] That their data do not give a representative picture is suggested by the fact that 66 per cent of their patients fall into the most serious and advanced group, with only 9 per cent of the entire series alive five to nine years after diagnosis. Earlier studies of prognosis employed varying diagnostic criteria. Some reports included patients followed from the date of the first symptom only, others whose course had already become complicated. Thus Janeway, using a systolic blood pressure of 160 mm. of mercury as his index, declared that hypertensives lived only an average of four or five years after appearance of their first symptom.[2] Blackford and Wilkinson grouped only those patients with arterial pressures of 175/100 or over and found that the majority were dead within ten years.[3] Even actuarial statistics[4] fail to give a true picture since subjects studied are predominantly male, in whom hypertension is less common than in women and in general runs a more severe course. It is difficult to obtain a real understanding of the true outlook in this disorder from the available data.

Because of increasing interest in more radical medical and surgical therapeutic measures, it seems timely to re-emphasize the long duration of hypertensive vascular disease in many patients. This study is concerned with a selected group of hypertensive patients whose benign course is in contrast with that pictured in most studies dealing with the natural history of hypertension. The difficulties inherent in attempting to anticipate the course of the disease are illustrated by this report.

CLINICAL MATERIAL

The records of fifty patients were analyzed. All were closely followed as outpatients in the Vanderbilt Clinic and on the wards of the Presbyterian Hospital. The basis of selection included repeated initial blood pressures in excess of 140/90 and at least ten years of subsequent observation. Only such patients were included who were without significant symptoms when first

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TABLE I

STATISTICAL DATA ON FIFTY HYPERTENSIVE PATIENTS FOLLOWED TEN YEARS OR MORE

	Name	Sex	Age When First Seen	Years of Observation	Initial B.P.	Latest B.P.	Cardiac Failure	Renal Failure	Cerebral Accident	Now Living or Dead	Final Comments
1.	W. F.	F	38	10	230/140	210/130	..	..	..	L	Living and well
2.	E. S.	F	49	10	150/90	170/100	+	..	..	D	Cardiac insufficiency first evident 9 yr. before death
3.	H. N.	M	55	11	140/98	220/110	+	..	+	D	Died following cerebral hemorrhage
4.	M. H.	F	33	11	268/160	295/170	..	..	+	D	Died following cerebral accident
5.	M. K.	F	41	12	240/120	220/130	..	..	+	D	Died following cerebral accident
6.	S. K.	F	35	12	185/100	260/140	+	..	..	L	Recent cardiac insufficiency
7.	E. E.	F	22	12	160/120	160/132	..	..	..	L	Living and well; 3 normal pregnancies after development of hypertension
8.	V. S.	F	36	13	170/110	200/120	+	..	..	D	Died of cardiac insufficiency
9.	M. H.	F	45	13	178/96	200/100	..	..	..	L	Moderate headaches
10.	J. K.	F	34	13	185/100	260/140	..	..	..	L	Living and well
11.	C. B.	F	38	13	170/100	170/90	..	..	..	L	Living and well
12.	M. S.	F	49	13	200/95	270/120	+	..	..	D	Died 11 yr. after first episode of cardiac insufficiency
13.	I. M.	M	32	13	180/140	230/120	+	..	..	L	Mild cardiac insufficiency 4 yrs. ago; no symptoms thereafter
14.	E. S.	M	53	14	185/115	240/130	..	..	..	D	Postoperative death
15.	S. M.	M	33	14	185/105	185/120	+	..	..	D	Died of myocardial infarction
16.	E. S.	M	53	14	185/115	210/130	+	..	..	D	Unexplained death 3 yrs. after development cardiac insufficiency
17.	E. W.	F	55	14	280/125	278/140	+	..	+	L	Recent cerebral accident
18.	L. H.	F	49	14	200/120	270/140	..	..	..	L	Living and well
19.	A. R.	F	48	14	158/96	215/105	..	..	..	L	Headaches, no other symptoms
20.	G. S.	F	33	14	155/100	225/125	..	..	..	L	Living and well
21.	M. T.	F	50	15	195/100	190/120	..	..	..	L	Hypertension known 13 yrs. before first visit; has never had hypertensive symptoms
22.	A. R.	F	35	15	160/90	140/110	+	+	..	D	Died in failure 7 yrs. after first cardiac symptom
23.	L. F.	F	38	15	200/120	165/100	+	..	..	L	Cardiac insufficiency for 12 yr.
24.	S. R.	F	37	16	230/130	275/145	+	..	..	D	Death attributed to arteriosclerosis
25.	A. D.	F	47	16	162/90	210/90	..	..	..	L	Living and well; never had significant symptoms
26.	R. T.	F	29	16	190/110	260/130	+	..	+	D	Died following cerebral accident
27.	A. W.	F	40	17	170/90	180/110	..	..	..	L	Living and well
28.	R. S.	F	20	18	144/100	200/114	..	..	..	L	Rare headaches; no other symptoms
29.	V. A.	M	30	18	170/100	180/120	..	..	..	L	Living and well
30.	M. H.	F	32	18	196/100	190/105	+	..	..	L	Recent ankle edema only
31.	S. B.	F	39	18	180/100	175/120	+	..	..	L	Exertional dyspnea for the past 4 yr.
32.	J. B.	F	50	19	170/100	120/85	..	..	..	L	Living and well
33.	E. P.	F	45	19	200/90	240/130	+	+	..	D	Uremia and cardiac insufficiency
34.	A. T.	F	47	19	165/100	200/100	..	..	..	L	Living and well
35.	L. T.	F	45	19	170/110	160/84	+	..	..	L	Recent ankle edema only
36.	F. M.	F	50	20	150/98	190/110	..	..	..	L	Occasional headaches only complaint
37.	D. C.	F	40	20	160/105	200/160	..	..	..	L	Moderate headaches; otherwise well
38.	J. R.	M	57	20	165/100	210/110	+	..	..	D	Unexplained death; never had hypertensive symptoms
39.	C. M.	M	48	21	180/120	170/100	..	..	..	L	Living and well

TABLE I.—(*Continued*)

	Name	Sex	Age When First Seen	Years of Observation	Initial B.P.	Latest B.P.	Cardiac Failure	Renal Failure	Cerebral Accident	Now Living or Dead	Final Comments
40.	A. C.	F	26	21	150/110	140/95	..	..	..	L	Living and well
41.	A. A.	F	43	21	170/100	195/100	..	..	..	L	Occasional headaches and palpitations
42.	M. S.	F	42	21	165/105	210/115	+	..	..	L	Mild cardiac insufficiency for past 3 yr.
43.	A. P.	F	45	22	200/100	250/100	..	..	..	L	No symptoms; slight cardiac enlargement
44.	L. H.	F	46	23	200/110	210/120	+	..	..	L	Well except for moderate ankle edema
45.	H. M.	F	38	23	165/115	160/95	..	..	..	L	Intermittent headaches; no abnormal signs other than hypertension
46.	V. R.	F	28	23	165/110	170/90	+	..	..		Rare headaches the only complaint
47.	A. K.	F	39	23	155/95	160/80	+	..	+	D	Died after cerebral accident; previously asymptomatic
48.	L. S.	F	30	23	180/120	200/110	..	..	+	L	Living and well 11 yr. after cerebral accident
49.	B. O.	F	43	27	185/120	190/100	..	..	..	L	Living and well
50.	G. L.	M	41	27	200/110	180/94	..	..	..	D	Sudden unexplained death after 27 yr. without symptoms
Total and Averages		M 9 F 41	42	17	182/108	204/115	22	2	7	L 34 D 16	

seen and who showed no evidence of cardiac, renal or cerebral involvement. A few patients in the series had mild headaches as their only complaint. All who were later shown to have a primary renal disturbance with secondary blood pressure elevation were excluded, as were those patients initially exhibiting more than minimal, transient albuminuria. The degree of hypertension in the group as a whole suggests that the disease had been well established prior to the initial observation.

RESULTS

The results are summarized in Table I.

Age. The average age at the time of first observation was forty-two years, the youngest patient in the series being twenty-two years of age and the oldest fifty-seven. The average age was only slightly higher for males (forty-four years) than for those in the series as a whole. Those patients followed until their death showed no major differences in their average age when first seen (forty-four years) in comparison with the group still living.

Sex and Race. Forty-one (82 per cent) of the patients were female and 9 (18 per cent) were male. The racial distribution was comparable to that of the average clinic population.

Years of Observation. The average length of observation was seventeen years, varying from ten years and three months to twenty-seven years and one month. Thirteen of the fifty patients were observed for a period of over twenty years and twenty-nine of the patients were followed for more than fifteen years.

Deaths. Sixteen (32 per cent) of the fifty patients died during the course of observation, the majority as a result of cardiac

complications or following a cerebral vascular accident.

Blood Pressure. A composite picture of the systolic and diastolic blood pressure trends is shown in Figure 1. Although there was considerable variation in individual

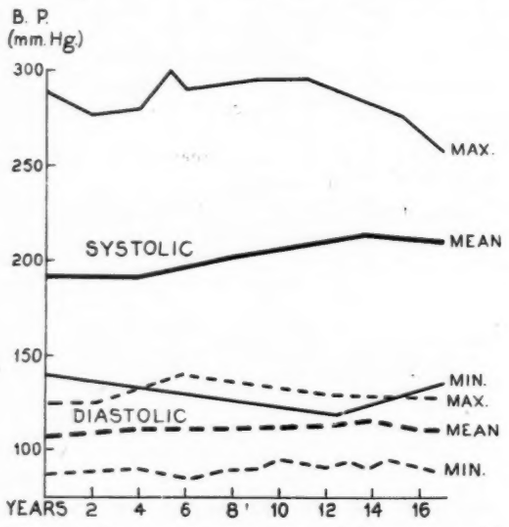

FIG. 1. Mean, maximum and minimum systolic and diastolic blood pressures of fifty hypertensive patients.

patients, the general tendency of the hypertension was to increase very slowly throughout the years of observation. The average initial blood pressure was 182/108 mm. of mercury while the average pressure at the time when last observed was 204/115. Blood pressure determinations were obtained during clinic visits by different observers and under varying conditions, hence evaluation of these readings should take into account personal variations in measurement.

Symptoms and Signs. These have been analyzed under the following headings with emphasis on their relationship to prognosis.

Patient's Complaints. A conspicuous number of patients during the course of their disease complained of fatigue, nervousness, dizziness, palpitation, insomnia and weakness in addition to specific symptoms to be further enumerated. There was no relation of these complaints to the subsequent course of the disease.

Cardiac Insufficiency. Twenty-two of the fifty patients at some time developed manifestations of congestive failure such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea and ankle edema. In most of these patients the insufficiency came late in the course of the disease. The average length of observation following the first onset of cardiac insufficiency was seven years, the longest period being fifteen years and eleven months. Eight (39 per cent) of this group with congestive failure died during the course of observation, the average age of survival from the first symptom being eight and one-half years.

Cardiac Pain. Nine (18 per cent) of the patients complained of pain of cardiac origin at some time. The average period of observation from the onset of pain was five years, the longest being nine years and five months. Only one of this group is still living.

X-ray Evidence of Cardiac Enlargement. Thirty-three (66 per cent) of the patients in the series showed an increased cardiac area by x-ray during the course of their disease. Of these, ten (33 per cent) died during the observed period, with an average survival of nine years. The average period of observation for the entire group from the first sign of enlargement was ten years, the longest being twenty years and three months.

Electrocardiographic Changes. Eighteen (36 per cent) of the fifty patients had electrocardiographic changes indicative of myocardial damage. Two of these changes occurred just prior to death. The average length of observation was six and one-half years, the longest being seventeen years and four months. Eight (43 per cent) of the group were followed until death with an average survival period of seven years.

Renal Changes. Only two patients showed evidence of nitrogen retention. One of these died from cardiac failure seven years later; the second patient died from uremia a few months after nitrogen retention was appar-

ent. Twenty-nine (58 per cent) of the fifty patients developed persistent albuminuria during the course of their disease. The average period of observation from the onset of albuminuria was seven and one-half years, the longest being twenty-seven years and one month. Eight (27 per cent) of the group died during the period of observation, the average period of survival being eight years.

Cerebral Changes. Seven cases (14 per cent) developed a cerebral vascular accident during the observed course of the disease. In six of these the cerebral involvement resulted in death. The remaining patient had a cerebral accident after twelve years of known hypertension and was without signs or symptoms for eleven years and was well when last seen in the clinic.

Retinal Changes. Thirty-three patients (66 per cent) had retinal changes of some degree during the course of their disease. The average number of years of observation from the onset of arteriovenous compression was ten years but it was present in one patient twenty-three years and five months before the date of the last observation. Eight (24 per cent) of the group died during observation with an average period of survival of nine years. Only seventeen (51 per cent) of the thirty-three patients with retinal changes developed more severe damage as indicated by hemorrhage, exudate or papilledema. The average period of observation in this group was six and one-half years but one patient survived twenty-one years and six months after extensive exudate had been seen. Nine (53 per cent) of this group died during observation, the average survival being seven years. There were several patients in the group showing retinal exudate and hemorrhages whose retinitis regressed conspicuously during the course of their disease.

Headaches. Thirty-seven of the fifty patients (74 per cent) complained of headaches at some time during the course of their disease. Most of these were of a minor degree and even the more intense headaches were not constant and often disappeared completely after months or years of great severity. It was of interest that a few patients, with no familial or previous history of idiopathic migraine, complained of headaches which assumed a typical migraine pattern. There was no correlation whatsoever between the frequency and intensity of the headaches, the height of the blood pressure or the course of the disorder.

Final Observations. Sixteen (32 per cent) of the patients in this series died, while twenty-four (48 per cent) were living and free of significant symptoms at the last observation. The remainder had more severe complaints or exhibited signs or symptoms of cardiac insufficiency.

COMMENTS

This series of fifty patients who were asymptomatic and had uncomplicated hypertensive vascular disease when first observed, and who were followed for at least 10 years, is obviously a selected one. It gives no consideration to hypertension in its more progressive forms or to patients who first consult their physician because of complicating signs and symptoms. Although the present study gives no statistical information as to its frequency, it does indicate, however, that long survival is not a rarity. The majority in this group showed well established hypertension at the time of initial observation and may have had an elevation of blood pressure for an indefinite period prior to observation.

Except for the mild character of their disease, the patients studied in this group appear to be comparable with other reported series of patients with respect to age, sex distribution and general characteristics. It is significant that in the group studied the initial level of the arterial pressure did

not seem to be associated either with symptoms, rate of progression or with the subsequent development of major cardiovascular complications. It was also apparent that palpitation, headaches, x-ray evidence of cardiac enlargement and retinal arteriovenous compression bore no correlation to the subsequent course.

A steadily rising blood pressure over a period of time, cardiac pain or insufficiency, electrocardiographic signs of myocardial damage, progressive renal damage, cerebral vascular accidents, retinal hemorrhages, exudate or papilledema were, in general, indicative of a relatively short life expectancy, but in individual patients a long period of survival followed such complications.

Thus, it is evident that in hypertensive patients, even in those who may complain of headaches, nervousness and palpitation, irrespective of whether there is cardiac enlargement, minor electrocardiographic change, minimal albuminuria and early retinal change, a definite prognosis should not be made since such a patient may live for one, two or more decades before fatal complications appear. Without repeated observations over a period of months or years, one is not justified in foretelling the future trend or in differentiating a relatively benign from a more malignant process. The indications for and the evaluation of the results of such procedures as sympathectomy must take into consideration the not infrequent long period of survival and comparative well being of many patients.

CONCLUSIONS

1. An analysis was made of fifty patients who, when first observed, exhibited asymptomatic and uncomplicated hypertensive vascular disease and were subsequently followed for at least ten years.

2. The average length of observation in this selected group was seventeen years, the longest period exceeding twenty-seven years.

3. It was found in the group studied that the initial height of blood pressure, symptoms such as headaches and palpitation, the presence of cardiac enlargement, minimal albuminuria, minor electrocardiographic changes and retinal arteriovenous compression bore no relationship to prognosis.

4. Essential hypertension may be compatible with many years of survival and well being.

5. The favorable outlook for some patients with hypertension should be considered in evaluating the indications for and the results of such therapeutic procedures as sympathectomy.

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Review

Clinical Aspects of Coronary Insufficiency*

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DERANGEMENT of function is responsible for the symptoms of disease and may exist without demonstrable anatomic lesions. Coronary insufficiency is a functional disturbance, associated most frequently with atherosclerosis of the coronary arteries and its sequelae. Less commonly, it is caused by syphilitic stenosis or occlusion of the coronary ostia, to aortic valvular disease or to a disorder in the rate or rhythm of the heart such as paroxysmal tachycardia. Indirectly, it can be brought about by a systemic disease of which severe anemia is an example. It is not dependent for its occurrence upon specific structural changes. It results when the blood delivered to the myocardium is inadequate, in quality or quantity, for effective performance of the work required of the heart. As a consequence of ischemia and anoxia, signs and symptoms appear which delineate various clinical pictures in a manner which serves to distinguish one from another.

In the discussion which follows, no attempt will be made to give an exhaustive survey. For a number of years clinical studies of coronary heart disease have been made in the Department of Cardiology at the Presbyterian Hospital. Some of these observations will be reviewed and correlated.

TERMINOLOGY AND CLASSIFICATION

To the various syndromes which may result from impairment of the coronary blood flow a variety of names has been applied. Their multiplicity has brought confusion rather than clarity and has increased the difficulties of accurate diagnosis. Angina pectoris, anginal pain, cardiac pain, coronary occlusion, coronary thrombosis, cardiac infarction, subacute myocardial infarction or necrosis, coronary failure and coronary insufficiency are designations employed loosely and, too often, in the absence of criteria that are sufficiently definite for differentiation. To insist upon a logical terminology is not mere quibbling; it is of basic importance. Without clear definition of terms, there can be no understanding of the conditions to which they are applied. As a result, diagnosis lacks precision and effective guidance of the patient is impossible.

The classification of disorders of the coronary arteries here presented is based upon disturbances of function and structure; both are concerned in determining the clinical features.[1] All types are regarded fundamentally as manifestations of coronary insufficiency so that a unity of concept is maintained. Because the disorders due to atherosclerosis comprise over 90 per cent of the entire group, consideration will be given only to them; but the principles involved apply also to those of different etiology.

Insufficiency of the coronary circulation may be divided properly into two main groups: acute and chronic. (Fig. 1.) The manifestations of the acute form are more dramatic and varied than those of the chronic variety and a larger share of attention has been given to them. From the point of view of management, the crucial point to be determined is whether recent infarction has occurred.

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The first subgroup of the acute variety comprises those cases in which no recent infarction has taken place and there is no evidence of recent coronary occlusion. The most common manifestation of acute coronary insufficiency of this type is the familiar paroxysm of anginal pain, but certain individuals are made aware of an impaired coronary blood flow by various pain equivalents. Among these are a sense of pressure or tightness across the chest, a sudden feeling of extreme weakness or, less commonly, profuse sweating, particularly about the head and neck. The symptoms sometimes are referred to the abdomen and are mistakenly regarded as due to some disorder of the digestive tract. Discomfort may be felt only in the shoulders, neck or back. In some cases, there is paroxysmal dyspnea without evidence of moisture in the lungs. In others, acute pulmonary edema accompanied by extreme dyspnea may result from the sudden onset of left ventricular failure. Sudden death may occur during sleep or following sharp exertion; or the heart may cease unexpectedly after excitement or emotion, whether this be pleasant or associated with grief or nervous shock. To this condition has been applied the term "acute, fatal coronary insufficiency."[2] The hearts of such patients show varying degrees of coronary sclerosis and narrowing but not necessarily evidence of recent thrombosis or infarction.

Infarction may be caused by rapid occlusion of a coronary branch or to marked narrowing of one or more branches which has been present for some time and which eventually leads to such a degree of malnutrition of the myocardium that softening takes place.[3] The most common symptom of acute obstruction is prolonged, agonizing pain, relieved only by large doses of an opiate. Often final closure is preceded by a succession of rapidly recurring anginal paroxysms, occurring even at rest, which furnish warning that occlusion is imminent. The diminished reserve of a previously impaired myocardium may be so far reduced by the added injury that congestive failure appears. Pulmonary edema sometimes ushers in the attack. As in the case of anginal pain, various substitution symptoms may mask the true nature of the basic pathologic process. Examples of these are mild substernal pressure, general weakness, sweating about the head and neck or nausea and vomiting; sharp epigastric pain may arouse the suspicion of an acute abdominal emergency. Shutting off of a coronary branch may be unaccompanied by any discomfort and may occur "silently," particularly in older persons debilitated by long-standing disease or in those suffering from surgical shock. Sudden death may result from ventricular fibrillation or standstill of the entire heart.

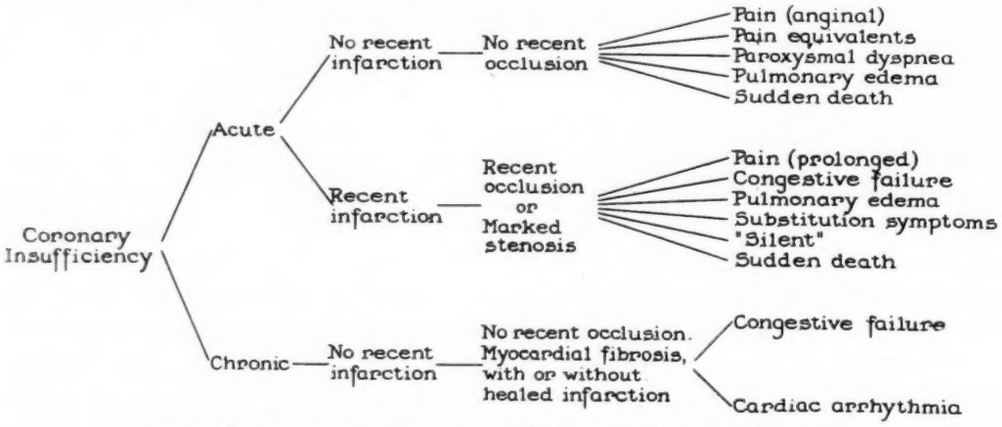

FIG. 1. Clinical types of coronary insufficiency and their manifestations.

In chronic coronary insufficiency, no recent cardiac infarction has occurred. There is extensive myocardial fibrosis and

not infrequently the heart muscle shows scars indicating the sites of healed infarcts. The patient may have had no symptoms and the lesions described are found at autopsy to the surprise of the clinician and the ill concealed pleasure of the pathologist. But often myocardial fibrosis leads to cardiac hypertrophy and to varying degrees of congestive heart failure. This clinical picture, formerly described as chronic myocarditis and subsequently as non-valvular heart disease, is produced by prolonged ischemia of low degree and consequent malnutrition of the heart muscle. Sometimes a cardiac arrhythmia, particularly auricular fibrillation or auriculoventricular heart block, affords evidence of a damaged and functionally disordered heart muscle.

It has already been said that the most important diagnostic problem for the clinician is to determine whether recent infarction of the myocardium has taken place. Its cardinal features are well known.[4] Fever occurs in almost every case, so that when the presence of a fresh infarct is suspected the rectal temperature should be taken and recorded twice daily for several days. Elevation of the temperature usually occurs on the second day and, in the uncomplicated case, persists, on the average, for a week. Increase of the sedimentation rate of the red blood cells likewise is a sign present in most instances; when the area of infarction is very small or congestive failure is present, the rate may be normal. The increase appears, as a rule, on the third or fourth day and persists for about four weeks unless some complicating condition, such as pulmonary infarction, causes a continued elevation. In mild cases, the sedimentation rate may return to a normal level within a week or ten days. Leukocytosis is observed earlier than the change in sedimentation rate, appearing often within the first twelve hours and almost invariably, if it occurs at all, in the course of the first day. It persists, on the average, for five days. Occasionally, no increase in the white count is found but slight rises above 10,000 per cu. mm. may be significant regardless of a corresponding relative increase in the polymorphonuclear cells.

Tachycardia and a fall in systolic blood pressure are found in over 80 per cent of patients. Changes in the form of the electrocardiogram are present in about 90 per cent if serial records are taken on successive days and several precordial leads are employed. In our experience, leads CF_2, CF_4 and CF_5 have been the most helpful when the diagnosis was in doubt. A gallop rhythm, or reduplication of the first sound at the apex, is heard in about 30 per cent of the patients. A pericardial friction rub is heard in only 20 per cent. It is often of short duration and may come and go in the course of the day. When present, it aids in diagnosis; its absence does not weight the evidence against the existence of infarction.

EVOLUTION OF CORONARY HEART DISEASE

If electrocardiograms are taken at frequent intervals in patients known to have coronary sclerosis, it is not uncommon to discover varying patterns without associated symptoms. Such an occurrence need not occasion surprise, for it is in accord with the concept that arterial degeneration is inherently a progressive process. Even several main coronary arteries may be occluded before the final illness in the absence of anginal pain or congestive failure. This has been clearly demonstrated by Blumgart and his associates who correlated the clinical manifestations with the pathologic lesions in hearts injected and dissected at autopsy.[5]

It has been possible to make a similar correlation between the course of the disease and the electrocardiographic pattern in patients who have been followed for long periods of time and who, while striking changes have occurred in the form of the graphic records, have experienced no discomfort. These changes may be progressive, indicating advancing lesions due to increasing impairment of the coronary bed, or regressive, pointing to the development of a

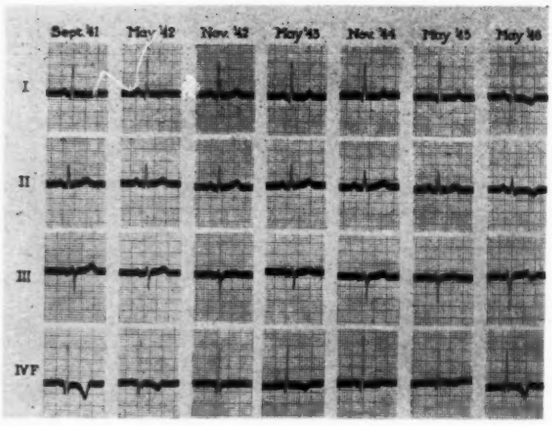

FIG. 2. Male, aged sixty years when first seen. Electrocardiograms show healing of cardiac infarct, instability of coronary circulation and occurrence of further occlusion, infarction and fibrosis. Patient asymptomatic throughout and leading an active life.

collateral circulation. Several instances of this sort have been reported in detail in an earlier paper.[6] In the following case a series of electrocardiograms portrayed, in turn, healing of a cardiac infarct, instability of the coronary circulation and the occurrence of further occlusion and infarction while the patient, unaware of these changing conditions in his heart, led a full and active life.

CASE REPORTS

CASE I. A. K., male, aged sixty years when first seen, was a business executive. He stated that he had an attack of coronary occlusion six months previously. His general health had been excellent and he never had any previous cardiac symptoms. He was in the habit of spending his vacation on his ranch in Colorado at an altitude of 7,800 feet where he rode horseback regularly, worked in the fields and never experienced any discomfort.

The symptoms of the coronary episode evidently were mild and pain was slight. He remained in a hospital for ten days and at home for ten weeks. Activity was gradually resumed and at the time of his first visit to the author, he was at work although at a slow pace. His only complaint was that following any unusual exertion, particularly after a meal, he felt a sense of substernal pressure.

The examination showed slight retinal sclerosis. The heart was not enlarged on percussion. The rhythm was regular; the rate was 60. The sounds were soft and a faint systolic blow was heard at the apex. There was also a short systolic murmur at the aortic area. The blood pressure was 154/86.

Orthodiagraphic measurement showed no cardiac enlargement. On fluoroscopic examination the border of the left ventricle appeared to be rather straight and the aorta was tortuous although not dilated. The electrocardiogram was characteristic of healed anterior infarction. (Fig. 2.)

The patient, who lives in a distant city, has been followed at intervals for the past five years. There has been no further discomfort in the chest. He has been working regularly, taking a brief rest on a couch each day after lunch. He has spent his holidays on his ranch and has ridden horseback. The blood pressure has ranged from 142 to 150 systolic; 80 to 88 diastolic. At the last examination, made a few months ago, he looked considerably younger than his sixty-five years.

A series of electrocardiograms showed interesting variations in view of the absence of any symptoms. (Fig. 2.) Between September, 1941 and November, 1942, there was a progressive trend toward normal. The T wave in lead I, which was inverted in the first record, became upright and T_{4F} became isoelectric. Small Q waves persisted in these same leads. In the records of May, 1943, November, 1944 and May, 1945, T_{4F} was variable, shifting from negative to positive and then to negative again although, during this period, the form of the limb leads remained constant. In May, 1946, striking changes were observed. The T waves in leads I, II and IVF were sharply inverted, indicating almost certain closure of a coronary branch located predominantly on the anterrio aspect of the heart, with infarction and subsequent fibrosis. At this time, he stated that he felt particularly well and could not recall having had any pain in the chest or a mild digestive upset even after direct questioning. A recent letter states that he has continued in good health.

DIAGNOSIS OF CORONARY INSUFFICIENCY

In no other disorder is a good history of more help than in the recognition of disturbances in coronary blood flow. Obviously, the efficacy of the blood supply to the myocardium cannot be measured directly;

the most reliable guide is the ability of the heart to perform its work, expressed in terms of the patient's sensations. No matter how well the story of disability is related by a medical colleague, it cannot give the same information as when it is obtained directly from the sufferer. The impression gained by the physician from careful questioning of the patient often furnishes the clue to the entire situation. In addition, such a personal interview establishes a relationship which is invaluable throughout the subsequent period of management.

The patient's account of his trouble may be the only available evidence on which to base an opinion since the examination not infrequently reveals no signs of disease. Sometimes the electrocardiogram shows changes which at once fix the site of the difficulty but here, as in the case of the history, the attending physician should make the interpretation. He must be aware of the wide range of the normal; too often a patient is advised to live as a cardiac invalid because of some minor graphic variation. On the other hand, the recognition of significant early abnormality may lead to preventive measures of vital importance. The use of multiple precordial leads has added to the accuracy of diagnosis in doubtful cases.

Cardiac enlargement, occurring in the absence of hypertension, valvular deformity or other obvious causes, should always arouse the suspicion of coronary disease. Unless enlargement is marked, percussion or location of the apex beat cannot be relied upon for the determination of the size of the heart and recourse must be had to orthodiagraphy or teleroentgenography. The establishment of normal standards for heart size, as indeed for any biologic variable, is difficult and the results are subject to error. Fluoroscopy often gives valuable information with respect to the size and shape of the various chambers and the character of their pulsations. In the author's judgment, the most useful measurement is the transverse diameter, as determined in the orthodiagram or teleroentgenogram, compared to the predicted transverse diameter computed by the Hodges-Eyster formula which takes into account the weight, height and age of the subject.[7] If the actual transverse diameter exceeds the predicted value by more than 1 cm., it is usually safe to infer that the heart is enlarged. A greater allowance is sometimes permissible when the subject is markedly obese and the heart is in an extreme transverse position. The cardiothoracic ratio, still sometimes employed, has been an unreliable index in our hands.

THE ANOXEMIA TEST

It is sometimes difficult to appraise the significance of pain in the chest and to locate its point of origin. The physical examination and electrocardiogram may fail to reveal evidence of cardiac disease. To determine whether the heart is the source of discomfort, because of an inadequate coronary circulation, is a matter of first importance.

We have been particularly concerned, in our laboratory, with the development of the anoxemia test.[8] This furnishes an objective index of the functional efficiency of the coronary circulation. It is based on the observation that induced oxygen want produces changes in the form of the electrocardiogram which are more pronounced in patients with coronary insufficiency than in normal subjects. Specific criteria have been evolved which make possible the distinction between a positive and a negative response.

Apparatus. A tank containing a mixture of 10 per cent oxygen and 90 per cent nitrogen furnishes an unvarying concentration of oxygen in the inspired air. The gas flows through a humidifier into a rubber bag which is kept full but not distended. Two flutter valves are incorporated into the system in such a way that rebreathing is avoided. A second tank, containing 100 per cent oxygen, is also in the circuit so that, if desired, anoxia can be quickly relieved by turning a needle valve.

Procedure. The subject is allowed to rest quietly in bed for a period of at least thirty

minutes. He is told that if pain is experienced in the chest, arms or abdomen during the test, he should at once raise his hand so that the test may be terminated. Electrocardiograms are taken with four leads; the standard leads and the precordial lead commonly designated IVF are used. The records are made just before the start of the test and at intervals of ten and twenty minutes thereafter. The standard period of inhalation is twenty minutes but if pain is felt or there are signs of an undesirable reaction, an electrocardiogram is taken at once and 100 per cent oxygen is then administered for one or two minutes. If distress is severe, 100 per cent oxygen is given immediately without waiting to take the electrocardiogram.

In each lead the deviation of the RS-T junction is measured in millimeters and the direction of the T wave is noted.

Criteria of a Positive Test. The result is positive when any one of the following is found: (1) the arithmetic sum of the RS-T deviations in all four leads (I, II, III and IVF) is greater by 3 mm. or more than in the control; (2) there is partial or complete reversal of the direction of the T wave in lead I, accompanied by an RS-T deviation of 1 mm. or more in this lead or (3) there is complete reversal of the direction of the T wave in lead IVF, regardless of any associated RS-T deviation in this lead.

Precautions. The control record should be developed and read before the test is begun in order to be certain that a recent cardiac infarct is not present. If there is doubt on this point, it is best not to proceed. In addition, the test should not be performed under the following circumstances: (1) if it has been done on the patient within the past twenty-four hours; (2) if congestive failure is present or (3) if cardiac infarction is known to have occurred within the preceding four months.

Unpleasant Effects. In the course of a series of studies of induced anoxemia, the test was given to patients with cardiac disease of different types and varying degrees of severity. Vasovagal attacks were occasionally observed. These consisted of slowing of the heart rate, fall in blood pressure, coldness of the skin, pallor and sweating. Mild convulsive seizures, dyspnea and hyperventilation were also noted in a few cases. Barnes and his associates have recorded ventricular premature contractions, nodal rhythm and brief cardiac standstill during the anoxic period.[9]

Acute pulmonary edema occurred in three of our patients with prompt recovery following the hypodermic injection of morphine, inhalation of oxygen and rest overnight. In three elderly patients with sclerotic cerebral vessels, there was mental confusion which lasted less than fifteen minutes.

In two of our patients, the physician in charge failed to read the control electrocardiogram before making the test. As a result, one of the patients died suddenly during the procedure. Both the electrocardiogram and the autopsy showed fresh infarction of the myocardium. In the second patient, ventricular tachycardia appeared after seven minutes of anoxemia. The arrhythmia persisted in spite of intramuscular injections of quinidine and oxygen therapy in a tent. Death occurred four hours later. In this instance, likewise, the control record clearly indicated a recent infarct. Autopsy was not done.

Results. In the Department of Cardiology at the Presbyterian Hospital, the test has been performed several thousand times. A detailed account of its use in 289 cases at the Mayo Clinic has been published recently by Pruitt, Burchell and Barnes.[9] It has been employed by the Medical Departments of the Army and Navy. At the New York Hospital, Stewart has had a wide and untroubled experience with it.[10] In Nylin's clinic, in Stockholm, more than 1,000 tests have been made; Biörck has published an account of 350 of these performed on 326 patients.[11] Data are accumulating rapidly from various sources.

In any large series of cases, the percentage of positive tests will depend on the nature of the material studied. Instead of quoting percentages, it seems more profitable to

make certain general statements which appear justified by the facts so far available.

A positive reaction may be regarded as a sign of coronary insufficiency. A negative reaction does not exclude disease of the coronary arteries. As is the case in any functional test, there must be a significant diminution in reserve before this can be demonstrated objectively. It cannot be too strongly emphasized that no clinical importance should be ascribed to a negative result.

In our experience, the occurrence of pain during a test which is electrocardiographically negative, is worthy of attention. If discomfort is similar in character to the original complaint, there is evidence that anoxia is capable of reproducing it. Follow-up of this group of patients has shown that a large percentage later developed unmistakable symptoms and signs of coronary heart disease. In many of them, the anoxemia test subsequently became electrocardiographically positive.

In the opinion of Barnes and his associates, pain induced by anoxemia is of no greater diagnostic value than the patient's description of his symptoms. This viewpoint is not supported by our studies. Obviously, the observer must make the distinction between pain of cardiac origin and the minor discomfort of an apprehensive subject. Usually this is not difficult. No significance should be attributed to the complaint of pain when payment for disability is involved.

The result of a test during which pain occurs but electrocardiographic changes are absent must be reported as negative. Patients in this category should be followed with special care and managed conservatively.

The test does not yield a quantitative expression of the degree of coronary insufficiency but in a given patient, there may be variations which parallel the clinical course. With improvement associated with the development of a collateral circulation, a positive test often becomes negative. Conversely, reduction in coronary flow may change a negative into a positive response.

It is not possible to predict, on the basis of the result, the likelihood of future coronary occlusion. The test affords an index, within undefined limits, of the adequacy of the coronary circulation at a particular time. When positive, it indicates a diminished coronary reserve. It yields no information concerning the nature or extent of the pathologic lesions in the heart.

If the precautions outlined are observed, the anoxemia test is a simple, safe procedure. With the proper selection of patients, even the mildly unpleasant reactions can be largely avoided. It has been shown to be of clinical usefulness in the differential diagnosis of coronary insufficiency. It has been employed also to study the effects of various drugs on the coronary circulation of man.[12] It does not require active cooperation on the part of the patient and anoxemia can be abolished promptly at any time by administering 100 per cent oxygen.

For routine clinical purposes, the anoxemia test should be restricted to those patients in whom the diagnosis of coronary insufficiency is in doubt. Only a positive result is significant.

The following case history illustrates the manner in which the test may aid in diagnosis:

CASE II. C. F., male, aged forty years, was an accountant. As a child, he had mild rheumatic pains in his knees and ankles which disappeared after tonsillectomy. He had never been seriously ill. He smoked thirty pipefuls daily and usually a cigar in the evening. He exercised spasmodically and never strenuously.

Two months before his first visit, he was awakened during the night by pain in the right shoulder which was gone by morning. A few days later, his car locked bumpers with another and an hour of vigorous exertion in cold weather was required to straighten out the damage. After this incident he noted pain in the right shoulder, right arm and right upper back when he walked rapidly. This gradually became less severe and was localized to the muscles in the upper portion of the arm. His physician suspected that the pain was cardiac in origin but did not test the effect of nitroglycerine.

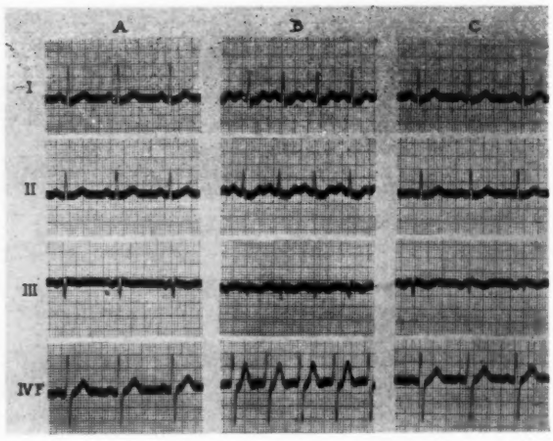

FIG. 3. Male, aged forty years, with pain in right shoulder upon effort. The clinical examination was negative. Anoxemia test indicates coronary insufficiency. A, control; B, after breathing 10 per cent oxygen for twenty minutes. The patient had slight pain in right shoulder after eighteen minutes. C, after breathing 100 per cent oxygen for two minutes; changes due to oxygen-want have disappeared.

On examination he appeared short and thickset. There was no retinal sclerosis. The heart was not enlarged on percussion. The rhythm was regular; the rate was 76. The sounds were of moderate intensity and clear. The blood pressure was 126/76. Fluoroscopic examination and orthodiagraphic measurement showed the heart and aorta to be normal in size and shape. The electrocardiogram showed left axis deviation and a prominent Q wave was noted in lead III.

The results of the anoxemia test are shown in Figure 3. The control record, in which the rate was 76, has already been described. After breathing 10 per cent oxygen for twenty minutes, he became somewhat cyanotic and the heart rate rose to 116 per minute. The changes in the electrocardiogram indicating coronary insufficiency are quite evident. There is partial inversion of the T wave in leads I and II, with depression of the RS-T segment in these leads as well as in lead IVF. He stated that at the end of eighteen minutes he felt pain in the right shoulder similar to that experienced on exertion, although it was somewhat less intense, so that he did not signal that he wished the test to be stopped. The final record in the series shows the disappearance of the changes caused by induced anoxemia after breathing 100 per cent oxygen for two minutes and room air for one minute. The heart rate at this time was 82 per minute.

The patient was relatively young and the results of the usual examinations were negative. The symptoms were suggestive but not characteristic of coronary insufficiency. The anoxemia test left no doubt as to the source of his discomfort.

THERAPEUTIC USE OF REST

It has become the fashion in recent years to disparage rest as a therapeutic measure in the management of cardiac patients.[13] Prolonged recumbency, it is said, leads to the development of thrombosis in the veins of the leg and hence predisposes to pulmonary embolism. It favors the development of hypostatic pneumonia in the aged. It shifts edema fluid toward the lungs instead of letting it gravitate to the legs. It causes hemodilution and increased blood volume as a result of the flow of fluid from the tissue spaces into the blood stream.[14] It has a bad psychologic effect for it encourages a state of cardiac invalidism. Finally, there is no good evidence, say these critics, that prolonged rest aids materially in promoting recovery.

It seems to the author that there has been too much criticism of the use of rest, particularly in the treatment of patients with coronary heart disease. There are many degrees of rest, ranging from complete inactivity in the recumbent position to merely the avoidance of athletic sports. There are different types of rest: physical, mental and emotional. So, too, there are numerous types of disorders caused by coronary heart disease and these, in turn, vary in severity. The age and psychologic make-up of the individual likewise play an important part in determining the physician's plan of management. With so many combinations possible, it is inconceivable that any standard regimen should best serve to accomplish the desired ends.

No one will deny that following severe, acute cardiac infarction, the patient should be kept quiet and in bed. The use of the commode instead of the bedpan, however, should be permitted early. There is no need to insist upon a flat bed after the stage of shock has passed; indeed, many patients who are not gravely ill prefer semirecumbency from the outset. Movements of the toes, feet and legs are encouraged; massage of the legs is given early and the position in

bed is changed frequently with the help of a nurse or orderly.

The circulation should be aided, whenever there are even slight signs of failure, by the administration of oxygen and the use of digitalis. We have proved to our own satisfaction that digitalis, given in the presence of an acute infarct, does not increase the likelihood of embolism, rupture of the heart or ventricular fibrillation. It accomplishes, in this condition, all that may be expected of it in a heart failing from other causes. It helps to abolish circulatory stasis.

The guidance of the patient during the periods of recovery and convalescence requires judgment and experience.[15] No laboratory test, such as the sedimentation rate, and no electrocardiographic criteria can be used to the exclusion of the clinical picture as a whole. Often, a persistent elevation of the sedimentation rate causes anxiety; allowing the patient out of bed is sometimes followed by a drop to normal.

It is easier, perhaps, to point out the possible dangers of rest than to gauge its benefits. Following cardiac infarction, those who are given adequate rest during the early weeks and months fare best in the years to come. That is an observation which, to the author, has seemed clear but it cannot be readily substantiated by scientific proof. Certainly, many whose outlook has seemed poor, after long periods of inactivity and freedom from business cares, have made a remarkably good functional recovery.

The same is true in some patients with frequently recurring anginal pain, induced by relatively slight effort or occurring even without it. They need not necessarily go to bed but weeks or months of freedom from any but minimal exertion and absence from customary responsibilities appear to aid in the development of a collateral circulation which eventually is adequate for the performance of ordinary amounts of work. From the point of view of dollars and cents, such a period of inactivity often proves to be an investment which pays large dividends.

Rest, like a drug, is a form of therapy which exerts its maximal effectiveness in amounts which are neither too large nor too small. There is a proper formula for each patient which must be adjusted to varying circumstances.

ACUTE, FATAL CORONARY INSUFFICIENCY

Disease of the coronary arteries is the lesion most frequently associated with sudden death. Occlusion, either thrombotic or atherosclerotic, is to be regarded as an episode in the course of sclerosis and is not essential for abrupt cessation of the heart beat.

In a series of 376 fatal cases of coronary sclerosis, with and without thrombosis, death was sudden in 14 per cent of the total number. But of the cases of sclerosis without thrombosis, death occurred in this manner in only 12 per cent whereas in the cases in which a thrombus was present, death was sudden in 33 per cent.[2] It appears that the occurrence of thrombosis almost triples the likelihood of a sudden end. This might be anticipated, for closure further seriously reduces the carrying capacity of vessels already impaired by narrowing and loss of elasticity.

That sudden occlusion of a coronary artery can cause the ventricles to fibrillate was demonstrated in animal experiments by Cohnheim[16] some sixty-five years ago but the mechanism concerned in death from coronary heart disease has been recorded infrequently in man. In 1939, Smith[17] collected four cases in which the electrocardiogram showed ventricular fibrillation and added one of his own. Since then, four others have been reported.[18] In these nine cases, autopsies were performed in only three instances. In two other cases, total standstill of the heart followed ventricular tachycardia without the appearance of ventricular fibrillation as an intermediate arrhythmia.[19]

It has been unusual then to record electrocardiographically the mechanism of the dying heart and to correlate the clinical picture with the autopsy findings. For this reason, the tenth proved instance of death due to ventricular fibrillation in a patient with coronary heart disease is here briefly presented. In this case, a tracing was obtained of the dying heart and a post mortem examination was made.

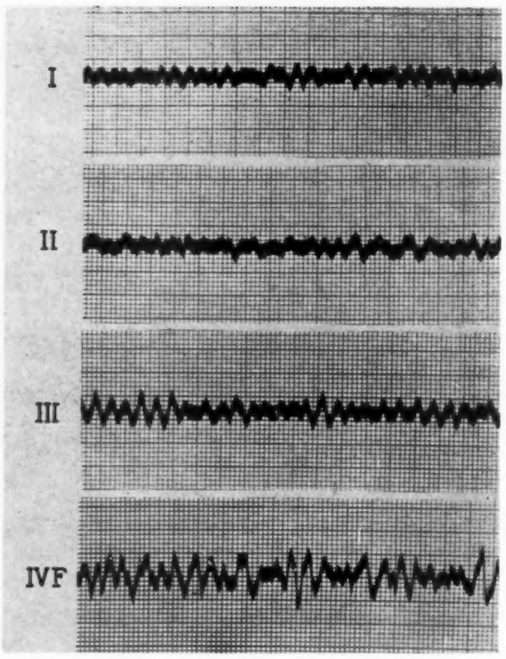

FIG. 4. Male, aged fifty-seven years. Sudden death occurred three hours after first symptoms of coronary thrombosis. Electrocardiogram shows ventricular fibrillation. Patient ceased breathing less than one minute after record was taken. At autopsy a fresh thrombus occluded the right coronary artery but there was no necrosis of the myocardium.

CASE III. G. A., an Italian born male, was fifty-seven years old at the time of his death. Nine years previously, a partial thyroidectomy was performed for diffuse toxic goiter, auricular fibrillation and cardiac insufficiency. It was noted then that his heart was enlarged. Following the operation, sinus rhythm was restored and the functional capacity of the heart was greatly improved. For economic reasons he resumed his work as a furniture mover and later was engaged by the city water department to dig trenches. He carried on this physical labor without discomfort.

On the morning of his death, he suddenly felt precordial and epigastric pressure which was not severe. When seen in the emergency room at the hospital, there were no signs of shock or of cardiac failure. The blood pressure was 136/96. The cardiac rate was 76; the rhythm was regular. A soft systolic murmur was heard at the apex. He was admitted to the overnight ward for observation and three hours after the onset of discomfort an electrocardiogram was taken. This showed ventricular fibrillation. (Fig. 4.) Less than one minute after the record was completed, he suddenly stopped breathing.

At autopsy the heart was found to be enlarged; it weighed 510 Gm. Both coronary arteries contained numerous small atherosclerotic plaques. The right coronary artery, 6 cm. below its origin and about in the middle of its course, was obliterated by a greyish thrombus which was firmly attached to the wall of the vessel. The myocardium of the right ventricle was pale but no gross necrosis was seen.

Microscopic examination of the heart muscle showed hypertrophy of the fibers and a moderate increase in interstitial tissue. There was marked intimal thickening of several of the coronary arteries. No evidence of necrosis was found in either ventricle. Most of the viscera showed congestion but no other significant changes.

In this case, sudden death due to ventricular fibrillation occurred three hours after the onset of symptoms of coronary thrombosis. Occlusion of the coronary artery apparently was so recent that no softening of the heart muscle had occurred. Acute coronary insufficiency induced the arrhythmia which caused death.

SUMMARY

Some of the clinical features of coronary insufficiency have been given brief consideration. A classification of the common types has been presented for the purpose of correlating diverse manifestations, all of which are caused by an inadequate coronary blood flow. The importance of recognizing infarction has been stressed. It has been demonstrated that atherosclerotic changes in the coronary arteries often progress insidiously and that, in many instances, processes of repair compensate adequately for the damages of disease. Some of the cardinal points in diagnosis have been discussed. Too little attention has been given to cardiac enlargement alone which, in the absence of hypertension, valvular deformity or other obvious causes, affords presumptive evidence of coronary heart disease. The use and limitations of the anoxemia test as an aid in the recognition of coronary insufficiency have been described.

Because prolonged rest in bed has been credited with certain undesirable effects on the circulation, the impression apparently has been created that the importance of rest, in general, in the treatment of cardiac ailments has been overemphasized. In the

author's opinion, there has been too much criticism of the use of rest. It is the most valuable single therapeutic procedure in the management of the patient with coronary heart disease. The fault lies not in the remedy but in lack of discrimination in its application.

Acute coronary insufficiency is the most common cause of sudden death. In the few cases of coronary disease in which the mechanism of the dying heart has been recorded, ventricular fibrillation usually has occurred just before respiration ceased. Less frequently, ventricular tachycardia has been followed by total cardiac standstill.

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Seminars on Hypertension

Experimental Renal Hypertension

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DURING the period in which any medical subject is actively investigated it becomes necessary from time to time to summarize what has been accomplished. This has been done on the subject of hypertension in several books and reviews[1–11] and much of this writing has been, of necessity, repetitious. This symposium, of which this discussion is merely the introduction, will also include much repetitious material, but it is written because it is hoped that it will reach many readers to whom previous publications have not been accessible and because it will include some new material. Few references will be given because extensive bibliographies are available in previous publications.[1–11]

It has now become customary to assign to Richard Bright the credit for the basic idea that hypertension may frequently be of renal origin. This has been done despite the full realization that Richard Bright never determined blood pressure in man and never proved that a state of hypertension actually existed. Certainly, he knew nothing of what is now termed essential hypertension. He did recognize, however, that the large, heavy heart found at autopsy in some patients, for which there was no other obvious explanation, was frequently associated with some abnormality of the kidneys. Bright related the increased weight of the heart to the disease of the kidneys in these patients and even suggested that a chemical substance in the blood, of renal origin, might have been the direct cause of the hypertrophy. He speculated that this was in all likelihood due to increased action of the heart and increased resistance to the onflow of blood brought about by a hypothetical chemical substance. The latter idea is certainly in keeping with the modern concept that increased peripheral vascular resistance is, under most circumstances, the basic mechanism of elevated blood pressure.

Although Richard Bright may be credited with lighting the torch, credit should also be given to those who kept it alight. Chief among those who kept the idea of the possible renal origin of some forms of human hypertension alive was Volhard[12,13] who believed that, at least in pale (malignant) hypertension, disease of the kidney played the important primary part in the pathogenesis of the elevated blood pressure. He searched for but failed to find a vasoconstrictor substance in the blood of patients in the malignant phase of essential hypertension. There are those who still deny that the kidneys ever play a primary part in the pathogenesis of hypertension, but it is now quite generally recognized that primary renal disease may be associated with human hypertension and that a causative relationship between the two conditions may exist. Few fail to accept the renal origin of hypertension associated with glomerulonephritis (acute and chronic), bilateral chronic pyelonephritis, bilateral polycystic disease of the kidneys, bilateral ureteral obstruction, renal amyloidosis and other conditions that involve considerable reduction of renal parenchyma. The existence of renal disease in such cases is

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usually determined by the accompanying abnormality of renal excretory function which is the direct result of the renal disease.

It is in the case of so-called essential hypertension that the primary renal origin of the elevated blood pressure is still held in doubt. In fact, essential hypertension by definition has been characterized as elevated blood pressure of unknown origin without recognizable disturbance of renal excretory function. A critical statistical analysis of the data on renal excretory function in patients with essential hypertension by Dalton and Newsom led them to conclude that some impairment of the ability to concentrate urine and to excrete phenolsulphonphthalein is always detectable. The fact that in the early stages of essential hypertension, and even for many years after the onset, renal excretory functional abnormality cannot be demonstrated and that it is often absent throughout the entire course of the disease, has convinced some investigators that most cases of essential hypertension are not on a renal basis. The arguments usually adduced against the renal origin of essential hypertension include the occasional failure to find at autopsy any significant intrarenal vascular disease or any other abnormality of renal tissue.

After the existence of elevated blood pressure in man had been discovered the fact that hypertension was the cause of the enlarged heavy hearts observed by Bright was fully realized. Although increased action of the heart has been established as a condition which exists in the state of hypertension, it is now generally regarded as secondary to the hypertension produced by increased peripheral vascular resistance. Increased volume of the blood, although it occurs in the state of plethora which may be associated with hypertension, has certainly been eliminated as the cause of hypertension in general and has not been found to exist in essential hypertension. The same holds true for increased viscosity of the blood which has been excluded as the primary cause of elevated blood pressure. The important problem that remains is the elucidation of the pathogenesis of increased peripheral vascular resistance which is now recognized as the determinant of the elevated blood pressure and for which there can be at least two explanations. The more obvious cause would seem to be the widespread organic disease of small arteries and arterioles, discovered by Johnson and by Gull and Sutton, which could be a mechanical cause of the increased peripheral resistance; but this view has never been supported by the demonstration of organic vascular disease so widespread as to determine a mechanical increase of peripheral vascular resistance. The other and more probable mechanism of increased peripheral vascular resistance could be peripheral vasospasm induced by a nervous or humoral (including endocrine) mechanism. The studies of Prinzmetal[14] and of Pickering[15] minimize the possible primary importance of neurogenic vasospasm and no convincing evidence has been adduced for endocrinogenic vasospasm as the general primary cause of essential hypertension. This does not exclude recognition of the existence of patients with hypertension resulting from psychoneurogenic stimuli, diminution of the sensitivity of the carotid sinuses, hyperepinephrinemia or abnormal pituitary function. Our own observations led us to experimental investigation of the possible renal origin of peripheral vasospasm.

EXPERIMENTAL PRODUCTION OF RENAL HYPERTENSION

Most of the experimental work on the production of hypertension that was done prior to 1928, with the idea that hypertension might be of renal origin, chiefly involved methods which were likely also to produce disturbance of renal excretory function. Among these were unilateral and bilateral nephrectomy, reduction of the amount of functioning renal tissue by resection, the effect of a nephrotoxic substance, irradiation with roentgen rays, occlusion of one or both ureters, acute compression of the kidneys, embolism, passive hyperemia due to constriction of the main renal vein,

permanent occlusion of the main renal artery, vein and ureter of both kidneys, arteriovenous anastomosis and occlusion of the main renal arteries. A few of these methods were followed by some elevation of blood pressure but in most of the experiments hypertension did not persist and, in most cases, there was no elevation of blood pressure, or the hypertension was fleeting and probably of nervous reflex origin. Contradictory results were obtained by different investigators using the same methods. None of the methods actually reproduced the anatomic or even the physiologic state of the kidneys in benign essential hypertension. If the hypertension persisted for any length of time, it was usually accompanied by renal excretory impairment with or without uremia.

The idea of producing hypertension by a disturbance of intrarenal hemodynamics was based primarily upon the observation, well known to pathologists, that intrarenal stenosing arterial and arteriolar sclerosis is found with great frequency in both the benign and malignant phases of essential hypertension. It was considered that the part possibly played by such a disturbance of intrarenal hemodynamics should be susceptible of experimental investigation. The most important of the working hypotheses of this study were: (1) If stenosing vascular disease limited to the kidneys, or any renal condition which produces the same effect on renal circulation, be the primary factor in the initiation of most cases of essential hypertension, then reproduction of the counterpart of the physiologic effects of such vascular disease, no matter how it might be accomplished, should result in the development of hypertension; (2) renal excretory functional disturbance should not be a necessary accompaniment of this type of experimental hypertension and (3) the probable disturbance of renal hemodynamics produced by intrarenal stenosing vascular disease might be reproduced by constriction of the main renal artery and, if the basic hypothesis be correct, should result in the development of elevated blood pressure. It was considered that fulfillment of all these conditions would answer the requirements of the definition of essential hypertension and signify the experimental reproduction of so-called essential hypertension.

It is granted that the best procedure would have been to reproduce the intrarenal anatomic abnormality, namely, arterial and arteriolar sclerosis localized to the kidneys, but there was no known way of doing this at the time and it has not yet been accomplished. Since the main effects of intrarenal arterial and arteriolar disease of the kidney are probably reduction of intraglomerular capillary pressure and alteration, possibly reduction, of blood flow to the functioning components of the kidney, it was considered that these two effects, and any other physiologic disturbances that might occur, might be produced by the permanent constriction (not occlusion) of the main renal artery by means of a clamp. It should be appreciated at once that the method decided upon was a compromise, that it does not mean that stenosing arteriosclerosis of the main renal artery was considered to be a frequent finding in cases of human essential hypertension, or that application of the clamp was considered to reproduce exactly the anatomical state of the kidney in essential hypertension. This incorrect interpretation has been made by a number of authors and investigators.

Details about the clamp and about the instruments used for its application have been given in previous publications[16] and as a result will be omitted from this discussion. The principal effects of the application of the clamp on the main renal artery will be merely summarized herein.

Effect of Constriction of One Main Renal Artery. It was soon found, and unexpectedly, that constriction of the main renal artery of only one kidney was sufficient to induce a rise of blood pressure within twenty-four to seventy-two hours after the application of the clamp. In the dog, the elevated blood pressure usually lasts from four to six weeks and, only exceptionally, for several months. The maximum rise is

usually reached in about one week and the blood pressure remains elevated at that level for another week, after which it gradually returns to normal. In the sheep, the goat and the rat, the elevation of blood pressure as a result of unilateral constriction of the main renal artery may last much longer than in the dog. In all these animals, removal of the one kidney with the main renal artery constricted results in a prompt return of the blood pressure to normal. These findings drew attention to the possibility that even human hypertension might be on a unilateral renal basis and the later finding that, in man also, removal of the one diseased kidney results in a return of the blood pressure to normal in those patients in whom the other kidney is normal.

Effect of Constriction of Both Main Renal Arteries. Constriction of both main renal arteries, either at the same time or after an interval, results in permanent elevation of the blood pressure. The same effect is produced by constriction of one main renal artery and contralateral nephrectomy. By this means persistent hypertension has been produced in the dog, monkey, rabbit, rat, cat, sheep and goat and the blood pressure has remained elevated in some dogs for more than six years. Cash and Wood[17] and we have shown that this is true hypertension because both systolic and diastolic pressures become elevated. In some of the animals, even when both renal arteries are constricted, the blood pressure tends to return to a lower level in several months, and increased constriction of the renal arteries is necessary to re-elevate the blood pressure which then often remains elevated for years.

Perhaps the most important finding, other than the elevation of blood pressure, was that in animals with persistent hypertension due to moderate constriction of both main renal arteries there was no significant alteration of renal excretory function. Mere disturbance of intrarenal hemodynamics, therefore, is sufficient to produce hypertension without disturbance of renal excretory function. Thus, the two most important of the working hypotheses of these experiments are satisfied. Although the direct application of these observations to man is perhaps not justifiable, yet these results do offer experimental evidence for the view that benign essential human hypertension, usually associated with intrarenal arterio- and arteriolosclerosis without impairment of renal excretory function, may also be of renal origin. Much evidence, to be summarized later, has accumulated in favor of this view.

As control observations, it has been shown that constriction of the splenic arteries, of both femoral arteries and even of the aorta below the origin of both main renal arteries is not followed by elevation of blood pressure. Constriction of the aorta above the origin of both main renal arteries does result in significant elevation of the blood pressure but this is evidently due to disturbance of the circulation to the kidneys.

There have been some attempts to minimize the importance of these experiments because the main renal artery in human hypertension is not commonly stenotic. This is admitted, of course, but it does not constitute a good reason why experimental constriction of the main renal artery should not be considered capable of reproducing the functional state of the human kidney in essential hypertension. Although Yuile[18] and Blackman[19] have actually drawn attention to the not infrequent existence of stenosing arteriosclerosis of one or both main renal arteries in association with human hypertension, it is important to emphasize that constriction of the main renal artery was an expedient resorted to experimentally because it was the only method that seemed likely to produce a circulatory disturbance of the kidney resembling the most probable effect of *intrarenal* stenosing arterial and arteriolar sclerosis. To regard the experimental type of hypertension as not exactly like human essential hypertension because the main renal artery of human beings with hypertension is not frequently stenotic, is to misunderstand the whole problem and the main purpose of the experimental procedures

which were used for the production of experimental renal hypertension. Recognition of the probable similarity of these two processes is necessary for proper understanding and evaluation of the contributions made by the great variety of studies carried out on animals with experimental renal hypertension.

It is well known that in some cases of human essential hypertension the fatal outcome is associated with and due to renal excretory failure. In some instances the renal excretory insufficiency is an initial accompaniment of the hypertension and the condition proves rapidly fatal with death from uremia. It is interesting that this condition may be reproduced at will in animals. If both main renal arteries are greatly constricted from the start or if moderate constriction is practiced at first and great constriction later, hypertension accompanied by variable degrees of impairment of renal excretory function results. This same effect can be produced by excessive constriction of one main renal artery with contralateral nephrectomy or contralateral ureteral occlusion. In those animals that develop great impairment of renal excretory function along with hypertension, fatal convulsive uremia occurs and, at autopsy, the small arteries and arterioles in many organs show pathologic changes which resemble those observed in the malignant phase of essential hypertension.

Thus, hypertensive states resembling both benign and malignant phases of essential hypertension have been produced experimentally in animals merely by varying the degree of constriction of the main renal arteries, with consequent alteration in the intrarenal hemodynamics, the exact nature of which has not yet been determined. The evidence that has accumulated to indicate that the benign and malignant phases of human essential hypertension may also be primarily of renal origin will be summarized in a latter part of this paper.

In some animals in which examination of the kidneys shows that the potential accessory circulation to the periphery of the kidney has become strikingly prominent, with large arterial vessels entering the cortex of the kidney from the various surrounding organs and structures, it has been demonstrated that decapsulation of the kidney and enclosure of one or both kidneys in a fish-skin condom frequently results in a reelevation of the blood pressure which persists. This type of membrane does not induce the development of a thick hull of connective tissue around the kidney (such as is induced by wrapping cellophane, collodion or silk around a kidney) but it does reduce the accessory circulation to the kidney and it is thought that this induces the reelevation of blood pressure. Cellophane, collodion and silk membranes (as employed by Page and others) have been wrapped around kidneys and elevation of blood pressure has been observed to develop weeks or months after the application of these membranes. The elevation of blood pressure in these animals has been considered to be due to perinephritis and the compression of the renal substance by the thick hull of connective tissue which develops around the kidneys. There is no proof that actual compression of the kidney occurs in these circumstances. In fact, there is no proof that the mechanism of the elevated blood pressure is not due to the scar tissue which also develops around the renal pedicle, with possible constriction of the renal artery, vein and even ureter of the kidney. Two indications of the possibility of these effects are the passive hyperemia (venous obstruction) and the hydronephrosis (ureteral obstruction) which, in some degree, are almost invariably observed at autopsy in such kidneys. More work should be done on this type of hypertension to settle this question. It is considered that the pathogenesis of the hypertension, even that resulting from application of a membrane, is similar to the hypertension which results from constriction of the main renal arteries. The one important drawback of the method is that impairment of renal function is an almost invariable accompaniment of the hypertension and that fatal

uremia (the malignant phase) is a common outcome.

Pathologic Changes in the Tissues of Animals with Experimental Renal Hypertension. The intrarenal pathologic changes which result from constriction of the main renal artery are directly dependent upon the degree of constriction of this vessel. In animals in the benign phase of hypertension produced by moderate constriction of the main renal arteries without accompanying renal excretory disturbance, the kidneys may show little if any gross or microscopic abnormalities. In the early period after constriction, variable degrees of cloudy swelling and even changes in the mitochondria of the lining epithelium of the tubules, especially of the proximal convoluted tubules, may be found although later no obvious anatomic changes are detectable. Pathologic changes in the anatomic structure of the kidneys are therefore not necessary for the production of the elevated blood pressure. As Selkurt[20] has shown, striking physiologic signs of tubular damage may sometimes occur without correspondingly striking histologic alterations in the kidney as a result of variable degrees of anoxia for variable periods of time. This must depend upon intracellular changes which are not detectable by the usual methods.

In some animals, even in the benign phase after several months, one kidney may be found atrophic although in the interval there was no significant disturbance of total renal excretory function. In such animals the other kidney is usually hypertrophic and both in gross and microscopic examination appears normal. In the malignant phase, advanced parenchymatous degeneration and even diffuse necrosis, with or without hemorrhage, may occur in one or both kidneys.

Even after six years of persistent benign hypertension in dogs, no significant pathologic changes have been observed in the intima of the aorta or of large or small arteries that can be considered a direct consequence of hypertension. Slight to moderate hypertrophy of the heart has been observed, and thickening of the media of the large and small arteries due to hypertrophy and hyperplasia of the muscle fibers also occurs but intimal sclerosis has not been observed. The results of the experiments on the benign phase of hypertension in animals has therefore afforded no proof for the view that hypertension by itself is a sufficient condition for the production of generalized, true, simple, intimal arterial or arteriolar sclerosis.

In dogs, monkeys, rabbits, rats, sheep and goats that have died in the malignant phase of hypertension, even when terminating fatally in as little as forty-eight to seventy-two hours, profound changes in the blood vessels have been observed. These changes are similar in all respects to those seen in the terminal phase of human malignant hypertension but are not to be confused with arteriolosclerosis. The gross manifestation consists mainly of petechiae throughout the gastrointestinal tract, in the gallbladder, the urinary bladder, pancreas, adrenals, brain, pericardium and myocardium. Similar lesions have also been observed in the adventitia of the aorta and of some of the larger arteries. Microscopically, the small arteries and arterioles are the seat of necrosis and fibrinoid degeneration, with or without vascular and perivascular inflammation characterized by exudation of polymorphonuclear leukocytes and some lymphoid cells. The necrotizing and inflammatory changes in the arterioles are identical with those observed in the terminal phase of malignant hypertension. These lesions have not been observed in the blood vessels of kidneys with a constricted main renal artery; but when one main renal artery is greatly constricted and the ureter of the other kidney is ligated, arteriolar lesions of the malignant phase may develop in the kidney with the occluded ureter in which intrarenal arterial tension was probably increased. It is considered, therefore, that the development of these necrotizing arteriolar lesions and especially of the petechiae, many of which are undoubtedly of capillary origin, requires

both the action of some chemical substance and the factor of increased tension. The pathogenesis of the arteriolar necrosis has been discussed in several previous publications but is still the subject of controversy. There are those who believe that hypertension *per se* is a sufficient condition for the production of these lesions but the unequivocal proof for this contention is still wanting. That elevated intravascular pressure alone is not a sufficient condition for the production of necrotizing arteriolar lesions is indicated by the fact that they are absent from the organs of dogs that for many years have had pronounced hypertension without accompanying disturbance of renal excretory function. This lesion has never been reported (and we have never observed it) in animals with experimental neurogenic hypertension of long-standing. This would certainly indicate that intense vasospasm alone is not a determinant of these lesions. Bilaterally nephrectomized animals with profound azotemia but without hypertension do not develop necrotizing lesions of the arterioles and associated petechiae. This indicates that the chemical factor alone is not sufficient for the production of the arteriolar lesions. That the lesions of the arterioles are not those of ischemic necrosis is shown by their absence from the ischemic kidneys of the animals and their presence in organs in which there is no obvious ischemia. The exact nature of the chemical substance or substances which play the important part in the production of the anatomic lesions has not yet been elucidated. Winternitz and collaborators[21] have been able to produce lesions of a similar nature by repeated injections of an extract of kidneys, but this does not prove that these chemical substances by themselves have the ability to produce these lesions and there is certainly no proof that the renin which was present in these extracts was the chemical substance responsible for the lesions. The vasculitis and perivasculitis are probably a reaction to the degeneration and necrosis of the walls of the arterioles or may be caused by the same agent that produces the necrosis. Lesions of arterioles similar to those of the malignant phase have been produced by the repeated intravenous injections of tyramine but this does not justify the inference that tyramine is responsible for the lesions of the malignant phase.

Malignant arteriolar lesions have been observed by Wilson and Byrom[22] and others in the contralateral kidney of rats with hypertension caused by constriction of one main renal artery. We have not been able to confirm these observations in dogs, rabbits, monkeys, sheep or goats with hypertension due to constriction of one main renal artery. That hypertension by itself is able to cause the characteristic malignant arteriolar lesions in an animal with hypertension due to constriction of one main renal artery has therefore not been substantiated in experiments on other animals. All the glomerular and interstitial inflammatory lesions, as well as the vascular lesions within an otherwise supposedly normal rat kidney, have been observed by us in the kidneys of rats with normal blood pressure. A possible explanation of the changes in the arterioles of the contralateral kidney observed by Wilson and Byrom and the others may be the fact that they were unaware of the frequent coexistence of hydronephrosis or pyelonephritis in one or both kidneys of adult rats. By constriction of only one main renal artery they may have been dealing, in some of these rats, with bilateral renal disease. There is, of course, the remaining possibility that the rat differs in this respect from all other animals.

Changes in Organs Other than the Kidney in Experimental Renal Hypertension. In experimental renal hypertension the pulse rate remains unaltered and there is no significant alteration in the output of blood from the heart. The blood volume in hypertensive dogs shows no significant alteration from the normal. The blood pressure in the lesser circulation (main pulmonary artery) is also within the limits of normal, indicating that the pulmonic vessels are not affected by peripheral vascular constriction. No signifi-

cant changes have been observed in the blood, with the exception of retention of nitrogenous products in the malignant phase. The pH of the blood remains normal in animals in the benign phase of hypertension. The lipid and protein content of the plasma shows no alterations but a slight increase of free cholesterol at the expense of the esterified fraction has been reported by Page. To this he has attached no special significance.

Animals in the malignant phase with retention of nitrogenous products also show retention of guanidine compounds, but no special significance has been attached to this pressor substance in the blood because it does not accumulate in the blood in the benign phase. A redistribution of the water content of skeletal muscles of dogs with experimental renal hypertension has been reported. This occurs mostly in the malignant phase and merely indicates some extracellular edema.

It is of interest that excision of the carotid sinus and of the cardiaortic nerves does not effect a lowering of the blood pressure in animals with constriction of the main renal arteries. We have found that excision of both carotid sinuses did not alter the development of hypertension produced by renal ischemia and that the level of blood pressure reached by such animals was no different from that of animals with intact carotid sinuses. It would seem that the regulatory system of the blood pressure functions actively in experimental renal hypertension and that it probably acts normally although at a high level. It has been found that animals with experimental renal hypertension react in hypersensitive fashion to injections of adrenalin, tyramine and pitressin, but no one has suggested that these substances play any part in the origin of the elevated blood pressure. On the contrary, Robbers and Westenhoffer[23] have concluded that tyramine cannot be the cause of experimental renal hypertension because they found that injection of cocaine causes no fall of blood pressure in hypertensive dogs. The dog's reaction to the cold pressor test has been found to be the same after the development of hypertension as in the prehypertensive state.

An interesting observation, confirmed by many investigators, is the fall of blood pressure in the hypertensive dog in the presence of an infection, especially distemper, with a return of the blood pressure to the initial level after the infection disappears. The slow return of the blood pressure to normal in the case of distemper is probably due to the slow recovery of the animals from this infection. Similar effects can be obtained by the injection of bacterial products, for example, typhoid vaccine injected intravenously. Whether this effect is produced by the dilatation of systemic arterioles and decrease of peripheral resistance, or by dilatation of afferent glomerular arterioles and increase of intraglomerular pressure, has not been established.

Pathogenesis of Experimental Renal Hypertension. As soon as the successful production of experimental renal hypertension had been accomplished, it was realized that this might afford an opportunity to determine the possible causal relationship between hypertension and the arterio- and arteriolosclerosis so frequently observed in association with hypertension in man.

The arteriolar sclerosis of the kidneys which has been reported by Fishberg,[24] Bell and Clawson[25] Moritz and Oldt[26] and others to be an almost constant necropsy finding in cases of human essential hypertension, has been interpreted by some as proof for the view that the hypertension comes first and that it is the cause of the renal vascular disease. Biopsy specimens of kidney obtained from the same individuals before and after the development of hypertension would, of course, help to solve this problem. There is no way of determining which persons will develop hypertension, and, for many other reasons, such a study of human beings is not possible. Biopsy specimens of kidneys in cases of established human hypertension have, however, been obtained by Castleman and Smithwick.[27] Their study did not lead to a solution of the problem and there is

certainly no good reason for accepting the conclusion of the authors that the results of their investigation show that the vascular disease is caused by or develops after hypertension. Study of a few arterioles in a minute specimen from the periphery of the cortex of the kidney can hardly afford any estimate of the hemodynamic state of the entire kidney. As a matter of fact, stenosis of one, large intrarenal artery could easily account for profound hemodynamic disturbances in a large mass of kidney substance supplied by thousands of arterioles that are not themselves diseased. Such intrarenal stenosing arteriosclerosis of large intrarenal vessels is a common finding in kidneys with vascular disease. It is the opinion of the author that the possible contribution of this obliterative sclerosis of the large intrarenal arteries, and even of the main extrarenal artery, to the disturbance of intrarenal hemodynamics has been underestimated. That extrarenal obliterative arteriosclerosis of the main renal artery can and frequently does occur in individuals with hypertension has been shown by Blackman.[19] This may or may not be accompanied by intrarenal arterial and arteriolar sclerosis. At no time has it been asserted by us that stenosis of the main renal artery, unilateral or bilateral, is a common cause of human essential hypertension or that experimental constriction of the main renal artery reproduces the anatomic state of the vascular system in the hypertensive kidney. However, when it exists, the part played by such obliterative sclerosis of the main renal artery cannot be denied and the effect of the clamp is regarded as reproducing the intrarenal hemodynamic disturbance of the kidney produced by the *intrarenal* arterial and arteriolar sclerosis, the condition commonly found in the kidney of patients with hypertension.

Production of the counterpart of the benign and malignant phases of human hypertension in animals has made possible investigation of the probable pathogenesis of hypertension in man. The following mechanisms may be involved in elevation of blood pressure: (1) neurogenic, with vasoconstriction due to afferent nervous stimuli from the nerve endings in the kidneys to the vasomotor centers or sympathetic ganglia; (2) afferent stimuli from the kidneys, with resulting output of an increased amount of some known internal secretion which produces vasoconstriction either by central or peripheral action; (3) the entrance into the circulation of a primary pressor substance of renal origin, or the formation of a pressor substance as the result of interaction of a renal substance with a substance or substances already present in the blood.

Neurogenic Mechanism. By elimination of various portions of the nervous system and constriction of the main renal arteries before or after the section or excision of the nerves, it was shown that experimental renal hypertension is not caused by a nervous reflex from the kidney affecting the vasomotor mechanism of the body. Since a nervous reflex originating in the kidney is not the cause of experimental renal hypertension, a humoral mechanism is probably at play. There are those however who, like Ogden,[28] concede that a renal humoral pressor mechanism initiates experimental renal hypertension but believe that this is later superseded by a neurogenic mechanism mediated through the sympathetic nervous system. This view has not yet been established but it deserves more investigation.

Endocrinogenic Mechanism. No one denies the existence of human hypertension of endocrine origin. Hypertension associated with pheochromocytoma of the adrenal and with pituitary basophilic adenoma or basophilism are cases of this kind. However, there is certainly no good reason for believing that essential human hypertension is of endocrine origin. In the case of experimental renal hypertension, it has been shown that hypophysectomy, thyroidectomy, gonadectomy and pancreatectomy have no significant effect in preventing or lowering experimental renal hypertension in the dog. It has also been shown that the only endocrine organ which may possibly play a significant, even if only a secondary part in experimental renal hypertension, is the

adrenal gland. The medulla of the adrenal plays no part in the origin or maintenance of the elevated blood pressure in experimental renal hypertension, but there is some indication that the adrenal cortex may be of secondary importance. Complete excision of both adrenals in the dog interferes with the development of hypertension due to constriction of the main renal arteries unless adequate supportive and substitution therapy is given. When only a small part of the cortex of a single adrenal remains, there is no interference with the development of experimental renal hypertension in the dog. If both adrenals of a hypertensive animal are removed, the blood pressure promptly falls to normal. There is some evidence that the mode of action of the cortical hormone is to influence the production of a pseudoglobulin in the blood which acts as a substrate for the activity of renin to form the pressor substance, hypertensin.

The production of hypertension in dogs[29] by ligation of the hilar adrenal vein and the grossly visible small arteries and veins at either the superior or inferior pole of only one adrenal (Victor[29]) has not been confirmed by those who have repeated this experiment. The significance of this contribution remains to be established.

The recent contributions of Selye to the subject of the hormonal factors in hypertension, including the so-called *endocrine kidney*, await confirmation and will not be discussed in detail in this paper.

Renal Humoral Mechanism. That a humoral mechanism might be responsible for the elevated blood pressure in experimental renal hypertension was first indicated by the effect of tying off the renal veins in dogs with the main renal arteries constricted adequately to produce hypertension. Although these animals developed uremia and died in two to seven days, at no time did they show any elevation of blood pressure. The gradual elimination of a possible primary part played by the nervous and endocrine systems also stimulated the search for a probable humoral mechanism of renal origin which might be responsible for the elevation of the blood pressure in this type of hypertension and possibly also in human essential hypertension associated with renal disease. Most of the recent contributions to this subject have dealt with the humoral mechanism, about which there are now two separate and distinct views: (1) that a kidney with a constricted main renal artery, or with any other pathologic condition which may bring about a similar disturbance of renal circulation, may be the source of a chemical substance which when it enters the circulation raises the blood pressure; (2) that the normal kidney is ordinarily the source of a substance which has the ability to prevent hypertension and that it is the absence, destruction or neutralization of this substance which results in elevated blood pressure (Grollman). Most of the evidence presented to date favors the former view but unequivocal proof for this view is still lacking.

The fact that interference with the blood supply to any other organ but the kidney does not result in either temporary or permanent elevation of the blood pressure and that constriction of the celiac axis, the superior mesenteric artery, the femoral and splenic arteries and even the aorta below both main renal arteries fails to raise the blood pressure can be adduced as evidence that the kidney is unique in this effect. It has been shown that azotemia alone is not a sufficient condition for the elevation of blood pressure because bilateral nephrectomy or anastomosis between renal artery and vein, although followed by profound azotemia, are not followed by the development of hypertension. Acute nephrosis with uremia due to various metallic poisons also rarely results in an elevation of blood pressure. The shunting of the venous blood of a unilaterally nephrectomized dog from its only kidney through the liver by means of a reversed Eck-fistula does not prevent the development of hypertension due to constriction of the main renal artery, nor does it lower the blood pressure in a hypertensive animal. This excludes any

important effect of the liver on the pressor substance of renal origin.

Direct demonstration of the probable existence of a humoral mechanism of experimental renal hypertension was given by the transplantation of a kidney to the neck or groin of a bilaterally nephrectomized dog or rabbit (Braun-Menendez and collaborators). When the renal artery of the transplanted kidney, with no nervous connection with the rest of the body, was constricted, a pressor effect resulted after the usual interval. Also, transplantation of a partially or completely ischemic kidney from one dog to the neck of a bilaterally nephrectomized dog resulted in an immediate temporary elevation of the blood pressure when the circulation to the ischemic kidney was restored. This indicated that some chemical substance capable of bringing about peripheral vasoconstriction had been released from the ischemic kidney into the circulation. Whether or not this substance in the kidney is itself a vasoconstrictor or whether it becomes a vasoconstrictor after entering the blood stream is not elucidated by this experiment. Demonstration that sudden release of a clamp kept for five to seven hours on the entire renal pedicle (artery, vein and ureter) was followed by a prompt elevation of the blood pressure is another indication of the existence of a humoral mechanism. Removal of a completely ischemic kidney from the body without release of the clamp on the pedicle and perfusion of the kidney with normal saline solution resulted in the demonstration of a powerful pressor substance in the perfusate when injected into the same or into another animal (Prinzmetal, Lewis and Leo).[30] It is now generally recognized that the chemical substances involved in all of these experiments are probably the same.

By use of the Läwen-Trendelenburg technic in the South American toad the presence of a vasoconstrictor substance in the blood plasma obtained from the renal vein of a dog with experimental renal hypertension due to complete constriction of the main renal artery was demonstrated. Most investigators failed to find pressor substances in the systemic blood of hypertensive dogs or of human beings with hypertension. There was also no effect of blood from hypertensive dogs on the tonus of surviving arterial rings (Wakerlin), but Solandt and collaborators[31] did observe a definite rise in the blood pressure of a bilaterally nephrectomized dog to which they gave a direct transfusion of blood from a hypertensive dog; and Braun-Menendez and Fasciolo observed a pressor effect in a normal dog as a result of the intravenous injection of 100 cc. of renal venous blood from the transplanted renal ischemic kidney of another dog.

Piperidomethyl-benzodioxane (933F) does not have greater effect on the blood pressure of a hypertensive animal than on that of a normal one, whereas in both normal and hypertensive animals, the effect of epinephrine is completely reversed by an injection of this substance. This indicates that the effective vasoconstrictor substance of the kidney is not sympathomimetic.

All of the investigations mentioned above pointed to a chemical agent of renal origin as the probable cause of the elevated blood pressure in experimental renal hypertension. The search for the hypothetical pressor agent began with the repetition of some old experiments made by Tigerstedt and Bergman[32] which had been confirmed by some and denied by others. They consisted of the demonstration of a substance in the crude saline extract of a normal rabbit kidney which was capable of inducing a pressor effect when injected intravenously into a normal rabbit. For this substance the original term, renin, suggested by these authors has now been accepted as the name of the basic principle of the humoral mechanism of experimental renal hypertension. The demonstration by Prinzmetal and others of the existence of a greater amount of this substance in the kidneys of dogs with experimental renal hypertension and of human beings with hypertension associated with nephrosclerosis should be confirmed

by the newer methods for extraction and testing of this substance. In early experiments, the difficulty was that renin, which seemed to present at least some of the basic requirements for the hypothetical pressor substance of experimental renal hypertension, lacked any vasoconstrictor effect when perfused in saline solution through the lower half of a toad or the leg or tail of a dog from which the blood had been washed out. Two groups of investigators (Braun-Menendez and collaborators and Page and collaborators) independently discovered that renin is not directly pressor and that although it is the key substance of the humoral mechanism its effect is due to the interaction with a substrate in the blood, with the resulting formation of an entirely new substance possessing vasoconstrictor and therefore pressor properties. To this latter substance the South American investigators gave the name hypertensin while Page and collaborators named it angiotonin. The term hypertensin is now generally accepted. As a result of these earlier observations, Landis, in 1940, wrote: "The evidence that renal ischemia raises the blood pressure by a humoral mechanism seems unassailable." However, even to this day, some observers have concluded that there is no peripheral vasoconstrictor substance in the blood of hypertensive animals.

Although there is general agreement that in the acute phase of experimental benign renal hypertension, in the malignant phase of experimental renal hypertension and in various forms of hypertension associated with renal insufficiency in man (such as eclampsia and acute glomerulonephritis), renin and hypertensin are demonstrable in the systemic blood, it has not been demonstrated that renin in appreciable quantity exists in the systemic blood of animals in the chronic benign phase of experimental renal hypertension or in human beings in the benign phase of essential hypertension.

Whether or not the normal kidney plays a part in the homeostatic regulation of normal blood pressure through the humoral mechanism of renal origin, which begins with the excretion of renin, is still not established, but evidence is accumulating that it may play such a part. It has been shown, for example, that in shock the secretion of renin is induced and it is thought that the low blood pressure which produces renal ischemia is the cause. Although the existence of renin was discovered only about four years after the discovery of adrenalin by Oliver and Schafer and although the possible relationship of renin to the rise of arterial pressure in hypertension was obvious to the original investigators, nevertheless more than forty years passed before the existence of this substance was fully established. One of the reasons for this was the failure of some investigators to corroborate the original findings of Tigerstedt and Bergman. Many investigators who attacked this problem were really dealing with putrefactive pressor amines, not with renin, when they obtained pressor effects from the intravenous injection of autolyzed but not of fresh renal pressed juice.

Renewed interest in renin arose with discovery of the method of producing persistent hypertension in animals by constriction of the main renal arteries. The existence of a substance like that of Tigerstedt and Bergman in crude and even in more purified extracts of kidney was quickly confirmed. It was shown, moreover, that, as already indicated, the physiologic effects on the circulation resulting from the intravenous injection of this substance are not really due to the renin itself, which is not a vasoconstrictor, but are caused by hypertensin, the effective pressor substance formed by the interaction of renin upon a substrate (α_2 pseudoglobulin) in the blood plasma.

Page and Helmer noted that when renin is incubated with plasma or with serum, angiotonin (hypertensin) is formed, but that continued incubation results in the destruction of the angiotonin. This led them to believe that the continued action of the renin was responsible for the destruction of angiotonin. Muñoz and his collaborators, however, showed that this inactivating

effect of renin could be eliminated whereas the capacity of the renin to produce a pressor substance remained unaffected. This led them to postulate the existence of another enzyme associated with impure renin to which they gave the name hypertensinase. Page and collaborators later conceded the existence of such an enzyme and coined the name angiotonase for this enzyme to correspond with their nomenclature. This is a hydrolyzing enzyme or group of enzymes with the ability to destroy hypertensin *in vitro*. It is present in the blood plasma, serum, laked blood corpuscles and extracts of organs, especially intestine, kidney, pancreas, spleen and liver. Intestinal mucosa is the richest animal source of this enzyme. Blood serum and plasma that are not hemolyzed contain only a relatively small amount. An enzyme exactly like hypertensinase in its chemical and physiologic properties may be extracted from various plants, especially from wheat bran (Gollan, Richardson and Goldblatt). The chemical and physiologic properties of this enzyme have been described in detail in other publications.

Various names have been suggested for the different constituents of the humoral mechanism but the tendency at the present time is to accept the terminology originally suggested by the South Americans:

Renin (an enzyme from the kidney which enters the blood stream through the renal vein and interacts with hypertensinogen).

Hypertensin (a polypeptide formed by the action of renin. It is the active vasoconstrictor substance).

Hypertensinogen (a globulin in the blood plasma upon which renin acts to form hypertensin).

Hypertensinase (an enzyme in the blood and in extracts of some organs capable of inactivating hypertensin).

The chemical and physiologic properties of the various constituents of the humoral mechanism have now been described in great detail in several publications and will not be included at this time. The details about the method of assay for the various constituents will also be omitted from this report.

Mechanism and Site of Formation of Renin. Little is known about the exact mechanism and site of formation or release of renin, despite the vast amount of work that has been done on the properties of the various constituents of the humoral mechanism in experimental hypertension. Even at the present time, there are those who, like Grollman, question the existence of preformed renin in the kidney and who consider that it is merely the product of autolysis *in vitro*. His experiments may merely indicate that in the renal tissue of the living animal there exists a renin precursor (prorenin) which is transformed into renin as it leaves the living cell and that the same transformation can also occur *in vitro*. Phenomena of this kind are known to occur in the case of other proteolytic enzymes of which trypsin is a good example.

Just what it is that occurs in the kidney with a constricted renal artery leading to the release or formation of renin sufficient to cause hypertension is not yet known. The observation of decreased oxygen consumption by the ischemic kidney or by ischemic renal tissue has been confirmed, but the significance of this phenomenon has been questioned on the ground that the reduction may have been due to the death of a certain number of cells and not to uniform interference with the function of living cells. The continuous inhalation of 100 per cent oxygen for forty-eight hours failed to lower the blood pressure of hypertensive dogs and the inhalation of 7 to 10 per cent CO_2 did not cause a greater rise of blood pressure in such dogs. This has been interpreted as unfavorable to the view of a hypothetical ischemic factor in the pathogenesis of experimental renal hypertension. Cruz Coke,[33] however, has concluded that tissue anoxia, especially renal, plays an important part in the humoral mechanism of renal hypertension. The demonstration that the cytochrome C concentration and the activities of cytochrome oxidase and succinic dehydro-

genase are greatly diminished in slices and homogenates of kidneys of hypertensive dogs may be subject to the same criticism as the experiments on oxygen consumption. The significance of these observations cannot be evaluated at the present time and more work should certainly be done in this field.

Most *in vitro* experiments on the origin of renin have indicated that it originates in the cortex of the kidney, and especially in the lining epithelium of the convoluted tubules. The finding that extracts of the aglomerular fish kidney contain no renin proved of no great significance because it was shown later that marine fish kidneys which do possess glomeruli also do not contain renin while the kidneys of fresh water fish do possess it in considerable amount. An explanation for this difference has not yet been found. Renin can be detected in the kidney of the dolphin which is a marine animal. The involuting tubular portion of the mesonephros of the pig embryo decreases while that of the developing tubular portion of the mesonephros increases, and renin cannot be extracted from kidneys in which the proximal tubules have been destroyed by sodium tartrate poisoning. These facts indicate that the convoluted tubules are the most probable site of origin (production and storage) of renin or at least of prorenin, if this exists. The exact nature of the stimulus which brings about the release of renin or prorenin has not yet been determined. The idea suggested by Page and his collaborators that reduction of intrarenal pulse pressure rather than decreased blood flow to the kidney is what determines the release of renin and the formation of vasoconstrictor substance depends entirely upon the demonstration of a pressor substance in the blood by perfusion of the rabbit's ear. This method is not accepted as a specific test for renin or angiotonin so it is questionable just what significance should be attached to these experiments. Even the assumption of a presumable change from intermittent to continuous pressure beyond the site of the afferent glomerular arterioles is not justified for the very reason that a pulse pressure in the glomerulus has never been proven. Braun-Menendez has stated unequivocally that "the idea that diminished pulse pressure within the kidney causes the liberation of renin has no solid experimental proof." The reduction of blood flow through the functioning components of the kidney (glomerular and peritubular capillaries) is another possible stimulus for the formation and release of these substances. That there is a reduction in the blood flow to the kidneys in most cases of essential hypertension affecting both kidneys equally, as well as in the early stages of renal hypertension, is an established fact but there is still some question as to whether permanent reduction of the blood flow is necessary for persistence of hypertension in animals. The answer to this question must await better and more direct methods than are available at present for repeated determinations of renal blood flow before and after constriction of the renal artery. Page and his collaborators have concluded that reduction of blood flow is not a necessary condition for the development of hypertension because, by indirect methods they have found that occasionally in animals no permanent reduction occurred in the blood flow to the kidney, despite a slightly increased blood pressure. For the demonstration of true renal ischemia, Chasis and Redish require that the ratio of renal plasma flow (diodrast clearance) to tubular excretory mass (maximum tubular secretion of diodrast) should be calculated since reduction of diodrast clearance alone does not necessarily mean renal ischemia. Smith and his co-workers consider that the available evidence favors the view that the renal ischemia so frequently observed in essential renal hypertension is a secondary event, and that the primary event is the circulation of a humoral substance of unknown origin which brings about efferent arteriolar spasm with progressive and parallel reduction in renal blood flow which they consider characteristic of essential hypertension. Others believe that the afferent arteriolar

spasm is due to hypertensin produced by renin in the blood, but in experimental renal hypertension this begins only after the renal artery is constricted; in man, therefore, it should begin only when the blood vessels (intrarenal arteries and arterioles) are stenotic.

Dock demonstrated the existence of a normally perfusable vascular bed in the kidneys of human beings with benign hypertension, especially when the perfusing fluid was kerosene, but this does not justify the conclusion that perfusion of blood through the kidney *in vivo* is normal in such individuals. Despite the obvious objection to the method, it is of interest that there was a great decrease in the rate of perfusion (even of kerosene) through the kidneys of patients with uremia due to arteriosclerosis, glomerulonephritis and pyelonephritis. Too little is known about the anatomy of the renal vascular bed and the effective circulation through the functioning components of the kidney to permit any conclusions from experiments of this kind about the effect of intrarenal stenosing vascular disease or of any other pathologic process capable of producing similar hemodynamic disturbances. The existence of intrarenal large arterial and arteriovenous anastomoses would nullify the value of most perfusion experiments. The recent studies of Trueta[34] indicate that such anastomoses do exist and that even on the basis of vasospasm, blood may be shunted away from the cortex in sufficient quantity to account for cortical ischemia.

The possible part played by the juxtaglomerular apparatus in the humoral mechanism of experimental renal and of human hypertension has not yet been determined with certainty. This anatomical structure, which is situated in the distal portion of the afferent arteriole of the glomerulus, has been described in detail by Goormaghtigh[35] and others. Goormaghtigh has reported an increase in the size of the juxtaglomerular apparatus and in the number and size of the afibrillar and sometimes granular or vacuolated cells of this apparatus in the kidneys of rabbits and dogs with renal hypertension. He has also concluded that the afibrillar and granular cells may have a local or even a general secretory or humoral activity and may therefore have a direct relationship to the hypertensive principle. Afibrillar cells are common in the normal kidney of the rabbit, but Goormaghtigh has found an increase in the number of afibrillar and granular cells in the juxtaglomerular apparatus of rabbits made hypertensive by constriction of the main renal artery. He thinks that the afibrillar cells are connected with the arteriolar tone and that the granular cells are the source of the pressor substance. Dunihue[36] and Kaufmann[37] have confirmed his findings and agree with his conclusions. Graef and Smith, however, have drawn attention to the great variation in the appearance of the arteriolar media and in the size and structure of the juxtaglomerular apparatus in normal man and animals and have cautioned that because of species differences (for example, the absence of granular cells in the kidney of man and dog), interpretation of the effects of ischemia must be contingent upon a more complete study of normal kidneys. The development of cytologic changes in the juxtaglomerular apparatus, interpreted by some investigators as indicative of endocrine activity, does not constitute convincing proof of the origin of an endocrine substance or precursor in this structure.

No direct convincing evidence has been offered to the present time that any special cells in the juxtaglomerular apparatus or preglomerular arterioles actually are the source of a chemical factor which constricts afferent or efferent glomerular or peripheral systemic arterioles. There is, therefore, no good reason as yet for accepting the view that this apparatus is the regulator of glomerular blood flow or the indirect cause of hypertension. The presence of renin in extracts of kidneys of developing pig embryos, in which a juxtaglomerular apparatus has not been identified, rather militates against this view. For the present it is best to

say that the functional significance of the juxtaglomerular apparatus in its relation to hypertension has not yet been determined with certainty.

The possible part played by the vaso-excitor material (VEM) and vasodepressor material (VDM) of Shorr and his collaborators[38] in the pathogenesis of experimental renal hypertension is yet to be determined. This subject will be discussed separately by Dr. Shorr in these seminars.

Shipley, Helmer and Kohlstaedt[39] have discovered a pressor principle in the blood of cats, dead as the result of certain undiagnosed natural causes, of D.D.T. poisoning, or of prolonged hypotension resulting from large withdrawal of blood. Intravenous injection of the plasma of such animals into cats bilaterally nephrectomized two days before caused a sustained elevation of blood pressure for as long as five hours but had on effect on normal cats. This effect occurred with or without anesthesia and even in the pithed, nephrectomized test animals. The new pressor principle appears to be distinct from renin, angiotonin, pepsitensin, hydroxytyramine or tyramine because of the difference in contour and duration of the pressor response and the difference in the conditions under which the response was observed. This principle was not found in the blood plasma of bilateral nephrectomized cats poisoned with D.D.T. in which prolonged hypotension had been produced by excessive bleeding or in animals made uremic by bilateral nephrectomy. It was not found in the blood plasma of normal living cats or of normal cats which had been killed suddenly by various means. They concluded that a moderately prolonged period of hypotension (with concomitant diminished blood flow and/or blood pressure within the kidneys) is necessary for the production of this pressor principle. They have not yet isolated this substance in pure form but have concluded that it appears to be a protein; it does not pass through a dialyzing membrane or ultrafilter and is heat-labile. The active substance is partly but not completely precipitated at pH 4 by saturation of the extract with sodium chloride or by 0.6 saturation with ammonium sulfate. Although it has been demonstrated that renin does appear in the blood in the state of hypotension due to excessive bleeding, the amount of renin present is not sufficient to account for the pronounced and sustained pressor action of the hypertensin produced by the renin in the amount of plasma used in the experiment mentioned above. Injection of a fresh solution of renin extracted from kidney, capable of producing hypertensin *in vitro*, did not cause the same marked or sustained pressor response in the pithed, bilaterally nephrectomized cat. The fact that this new pressor substance produces such a sustained effect is of great interest. There does not appear to be any obvious connection between this pressor substance and the substances described by Shorr and his collaborators. The significance of this contribution to the problem of the humoral mechanism of hypertension and the regulation of normal blood pressure remains to be determined.

On the basis of experiments on renal hypertension in the rabbit, Pickering has concluded that only the initial phase of this type of hypertension is due to the renin-hypertensin mechanism and the persistence of the hypertension is not due to a neurogenic mechanism, as proposed by Ogden, but to another humoral mechanism. Because the pressor substance involved in the latter is not of renal origin, it is not identical with that of Shipley and his collaborators. More work is required before the exact nature of the mechanism involved in the acute and chronic phases of experimental renal hypertension can be considered established.

Antirenin. The entire subject of antirenin is a separate chapter which will not be discussed at great length here because it is not yet established that antirenin is specifically responsible for the antipressor effects originally described by Wakerlin and his collaborators.[40] These investigators found that in the serum of rabbits, dogs and guinea pigs (but not of the horse) injected subcu-

taneously or intramuscularly with renin from various species (not with homologous renin) a substance develops in the blood which is capable of neutralizing *in vitro* the acute pressor effect of an intravenous injection of renin. They regard this principle as analogous to an antibody, antienzyme or antihormone and suggested for it, the name antirenin. The injection of heat-inactivated homologous or heterologous renin does not induce the formation of antirenin in either normal or hypertensive dogs. After a normal or hypertensive animal has developed a high titer of antirenin large doses of homologous or heterologous renin may be injected intravenously without producing any change in the blood pressure. Wakerlin and his collaborators and we have found that repeated injection of heterologous renin subcutaneously or intramuscularly into hypertensive animals causes a fall of blood pressure to normal within a period of several months and that similar injections into normal animals for several months will prevent the development of renal hypertension when the renal arteries are constricted. Although he was the first to produce antirenin and was inclined at first to attribute these effects to antirenin, Wakerlin now considers that antirenin is not responsible for the prevention or cure of hypertension. We consider that the evidence on which he repudiates the significance of antirenin is not conclusive. This phase of the problem requires more investigation.

The possible application of the results obtained in animals to the treatment of human hypertension is beset with the difficulty that homologous renin does not induce the development of antirenin and the fact that human beings respond with a pressor effect to the intravenous injection of only homologous (human) renin.

SUMMARY OF THE SIMILARITIES AND DIFFERENCES BETWEEN ESSENTIAL HYPERTENSION IN MAN AND EXPERIMENTAL RENAL HYPERTENSION

Under this heading I can do no better than to repeat practically verbatim what I have already written under the same title before.

In two recent books on the subject of experimental hypertension, divergent views were expressed about the mechanism of elevation of the blood pressure. Goldring and Chasis[5] concluded that the weight of the evidence was against identity of the primary mechanism in human essential and experimental renal hypertension. They postulated the existence of a primary humoral mechanism of unknown origin to which a renal component may contribute a secondary and accessory effect. Braun-Menendez and his collaborators,[8] including Dexter who recently translated their book into English, have adopted the view that human essential hypertension in both the benign and malignant phases is primarily of renal origin. The existence of many similarities between any two processes or substances does not necessarily prove their identity, but I believe as they do that experimental renal hypertension faithfully reproduces human essential hypertension in most respects and that, for the present at least, it may be well to entertain the view that essential hypertension in man may be of renal origin.

In both types of hypertension there may be no significant disturbance of renal excretory function (the benign phase); or there may be pronounced renal excretory functional disturbance with uremia (the malignant phase), depending entirely, in experimental hypertension, upon the degree of constriction of the main renal artery. The malignant phase of human hypertension also may be directly dependent upon the severity and distribution of the sclerosis and stenosis of the intrarenal arteries and arterioles. Although an increase in the concentration of guanidine in the blood has been demonstrated in the malignant phase of hypertension in animals and man, this has little or no significance in relation to the cause of the hypertension because it occurs also in bilaterally nephrectomized animals that have azotemia but no elevation of blood pressure. In both types of hyper-

tension, cardiac action is increased but cardiac rate and output, volume, viscosity and peripheral flow of blood and venous pressure remain unaltered. In both man and animals, pulmonic arterial pressure also remains unaltered when the hypertension is uncomplicated by left ventricular failure as indicated by a normal right heart. In the benign phase of hypertension in both human beings and animals, cardiac hypertrophy chiefly involving the left ventricle develops. Medial hypertrophy of the aorta and arteries also occurs in both man and animals. In the malignant phase of both, essential hypertension in man and experimental renal hypertension in animals, many organs show the same typical vascular lesions (arteriolar necrosis, fibrinoid degeneration and necrotizing arteriolitis) which are recognized as characteristic of this condition.

The response to medical treatments of great variety is practically the same in both human and experimental renal hypertension. In both types of hypertension the blood pressure tends to go to higher levels with gain in body weight. The effect of a high protein diet is still undetermined. In both man and animals, hypertension associated with unilateral renal disease may be cured by excision of the diseased kidney, provided the other kidney is normal. Bilateral nephrectomy does not result in a rise of blood pressure in either man or animal, this despite the rapidly developing, profound azotemia. Sympathectomy, partial or extensive, may result in at least a temporary fall of blood pressure in human hypertensives without affecting the cause of the primary hypertension but there is little or no effect as a result of this procedure in animals. Whether or not this difference exists because the dog does not assume the erect position, with its consequent hemodynamic effects on the vasomotor apparatus, cannot be stated with certainty at the present time. The fact that after sympathectomy the blood pressure falls profoundly in some cases only when the patient is in the vertical position, that it rises again when the horizontal position is assumed and that it returns to the original high level in a considerable number of hypertensive patients, favors the probability of a renal humoral mechanism in which the vasoconstrictor substance is presumed to act directly on the musculature of the peripheral arterioles and not by way of the vasomotor nerves. This is in keeping with the conclusions of Prinzmetal and Wilson[14] and Pickering[15] as a result of their studies on the pathogenesis of human hypertension.

The frequent fall of blood pressure which appears in the late stage of pregnancy in animals with experimental renal hypertension remains as unexplained as a similar fall which has been observed by obstetricians in some hypertensive, pregnant women. The observation of polydipsia and polyuria in rats with experimental renal hypertension has not been emphasized in human hypertension and has not been reported in hypertensive dogs although the diuretic effect of renin injected intravenously into dogs has been mentioned.

Renal blood flow is reduced in most cases of human hypertension and in experimental renal hypertension. The direct studies of blood flow through the human kidney do not demonstrate clearly the physiologic effect of sclerosis of the afferent arterioles because the presumable vasospasm of the efferent arterioles, which results in a high glomerular filtration fraction, tends to mask the sclerosis. Although the interference with afferent blood flow is definite in animals and obviously brought about by constriction of the main renal artery, the same indirect signs of efferent vasospasm and increase of glomerular filtration fraction have been reported in hypertensive animals. In both humans and animals, this effect may be secondary to the primary humoral mechanism of renal origin which results from the hemodynamic disturbance produced by the preglomerular vascular disease.

The existence of renin has been demonstrated in the renal venous blood of ischemic kidneys of both humans and animals and the intravenous injection of renin or hyper-

tension gives the same indirect evidence of efferent vasospasm. In acute hypertension, whether benign or malignant, renin has been demonstrated even in the systemic blood of dogs and in patients with hypertension due to acute glomerulonephritis or eclampsia. The failure to demonstrate it in the systemic blood in human and experimental renal hypertension in the chronic benign phase may be attributable to the amount of blood used for the tests being inadequate or to the lack of sensitivity of the method for its detection. Whether the humoral mechanism is effective in only the relatively acute stages of hypertension and whether, as has been suggested, there is in the later stages a greatly increased sensitivity to hypertensin; whether another humoral mechanism is involved or whether the later stage of the hypertension is on a neurogenic basis, remains to be determined. Comparison of the pharmacologic effects of renin and the circulatory dynamics in hypertensive animals shows a parallelism that is striking but this does not mean that the chemical mediation of hypertension by means of renin has been proved either for animal or man. The participation of other pressor substances, such as epinephrine, tyramine, pitressin and guanidine, can be excluded from serious consideration.

Although the elevated systolic pressure of hyperthyroidism in man is relieved by thyroidectomy, thyroidectomy has no effect on essential human or experimental renal hypertension. It is doubtful that any of the known endocrine organs play a primary part either in essential hypertension associated with vascular disease in man or in experimental hypertension in animals. There is no definite evidence for the view that the hypophysis plays a primary or secondary part in the pathogenesis of renal hypertension, but there are definite indications that the adrenal cortical hormones do play a secondary part in the development and maintenance of experimental renal hypertension and perhaps of human hypertension. In experimental renal hypertension, the adrenal cortex plays its part presumably by influencing the production of hypertensinogen. This action is evidently exerted by an effect on the liver which is probably the source of this protein.

The many similarities between human essential hypertension associated with renal vascular disease and experimental renal hypertension suggest but do not prove that the former may also be of renal origin. Even if the renal origin of this form of hypertension should become established, it would still remain necessary to determine the cause of the arterial and arteriolar sclerosis which, when it affects the kidneys to a sufficient degree, initiates the humoral mechanism of the hypertension. The failure of animals to develop widespread arterial and arteriolar sclerosis, even after years of hypertension without accompanying impairment of renal excretory function (the benign phase), does not lend support to the view that hypertension is a sufficient condition for the production of vascular sclerosis. It must be admitted, however, that this may mean only that the blood vessels of animals are less sensitive than human vessels to the effect of increased intravascular tension alone although they appear to be even more sensitive to the conditions which determine the necrotizing vascular changes of the malignant phase of hypertension. Because the probable primary significance of renal arterial and arteriolar sclerosis has been indicated by experimental studies, the cause of vascular disease has now become the most important problem in the future investigation of the pathogenesis of hypertension.

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Participation of Hepatorenal Vasotropic Factors in Experimental Renal Hypertension*

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THE purpose of this paper is to supplement Dr. Goldblatt's review of experimental hypertension in this seminar with a consideration of the evidence obtained in this laboratory for the participation of recently described vasotropic principles of renal and hepatic origins in experimental renal hypertension.[1-3]

Our studies grew out of the important contribution of Chambers, Zweifach and their associates[4] to the significance of the vascular reactions of anesthetized animals subjected to prolonged hemorrhagic hypotension or traumatic procedures. By direct visualization of the peripheral blood vessels in the mesentery and omentum of animals in whom hemorrhagic and traumatic shock was induced these investigators were able to recognize two consecutive stages in the shock syndrome which are characterized by opposite types of vascular behavior. The initial compensatory phase was apparently related to a reduction in blood volume, the subsequent decompensatory phase to the period of inadequate peripheral blood flow. The reaction of the peripheral vascular apparatus to blood loss *per se* was found to be essentially compensatory in nature—an attempt to reduce the capacity of the vascular tree without drastically curtailing the blood supply to vital tissues. This compensatory response is characterized by a hyper-reactive condition of the peripheral blood vessels as evidenced by an increasingly enhanced reactivity of the terminal muscular vessels (the metarterioles and precapillaries) to epinephrine and an increase in their spontaneous vasomotor movements. This type of heightened reactivity persists even when the blood loss is sufficiently acute to precipitate collapse of the animal. Resultant capillary ischemia and restriction of peripheral blood flow to the most direct thoroughfare channels, the metarterioles, serve to maintain an active venous return of blood from the tissues until shortly before death. With prolongation of the profound hypotensive state, hyperreactivity was gradually superseded by a state of hyporeactivity, characterized by a progressive decrease in epinephrine reactivity and by slowing and finally complete cessation of spontaneous vasomotor caliber changes in the terminal arterioles and precapillaries. Loss of these restraining compensatory influences on peripheral circulation results in diversion of increasing amounts of blood into the capillary side channels from which it is inefficiently returned to the active circulation. This, in turn, leads to eventual failure of the venous return to the heart and to peripheral circulatory collapse. Once the hyporeactive stage has fully developed, transfusions are only of transient benefit, a state of irreversibility to replacement therapy having been reached. That blood-borne

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factors were responsible in large measure for both the compensatory vasoexcitor and the decompensatory vasodepressor effects was evident from the passive transference to anesthetized normal rats of effects corresponding to the reactions of the terminal blood vessels in the mesentery of the shocked animal at the time the blood sample was obtained.[5]

Vascular and humoral changes in the course of the development of experimental shock are summarized in Figure 1.

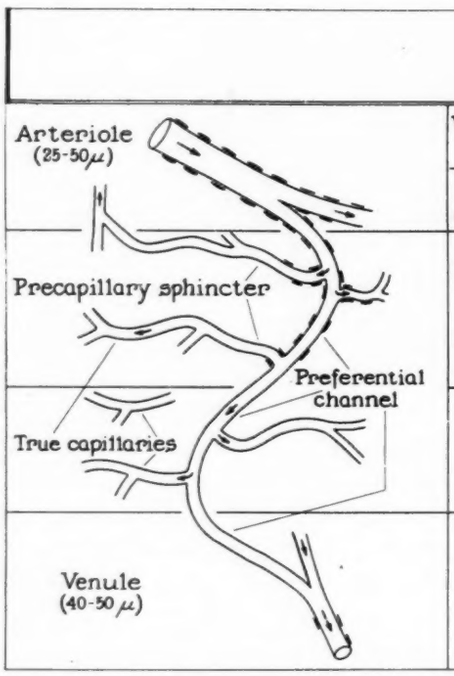
The significance of these observations lies in the demonstration of a constant participation in the shock syndrome of blood-borne vasotropic principles with specific actions on the terminal vascular bed, of such a character as to suggest that they are causally related to the initial compensatory vascular reactions to blood loss in the case of the vasoexcitor (VEM) and, in the case of the vasodepressor (VDM), to the progressive vascular deterioration which eventually results from prolongation of extreme hypotension.

This important contribution to the concept of shock provided the stimulus for laboratory studies which were designed to explore this concept further and, specifically, to investigate the sites of origin of these vasoexcitor and vasodepressor principles as well as the mechanisms leading to their formation and destruction.[6,7] These studies have involved a combination of *in vivo* and *in vitro* procedures whose correlation was made possible by utilization of the rat meso-appendix technic of Zweifach and Chambers[5] for the detection of vaso-excitor or vasodepressor activity in blood or tissue extracts. By means of this procedure in which the mesentery, specifically the meso-appendix, of the anesthetized rat is exteriorized for visualization it is possible to quantitate the extent of vasoexcitor and vasodepressor activity. This is done by determining the *degree* to which the response of the terminal vascular bed to the topical application of epinephrine is enhanced, as in the case of VEM, or depressed, as in the case of VDM; and further by noting the *duration* of these alterations in epinephrine reactivity.

Sites of Origin of VEM and VDM. The initial group of experiments was designed to trace the tissue origins of these vasotropic principles and to determine whether they represented products common to all tissues exposed to the relative anoxia prevailing in shock or whether their formation was limited to specific tissues. Experimental hemorrhagic and traumatic shock was induced in dogs, rabbits and rats. At appropriate times during the compensatory and decompensatory phases of the shock syndrome a variety of tissues was removed and prepared for study as for microrespiration experiments. These tissues included the liver, cardiac, skeletal and smooth muscle, kidney and spleen. Saline extracts were prepared and assayed by the rat meso-appendix method.

Bio-assays of tissues removed during the compensatory, hyper-reactive stage of shock, at a time when significant amounts of VEM had appeared in the blood stream, showed that the genesis of VEM could be related only to the kidney cortex, the saline extract of which invariably contained considerable amounts of this factor. The saline renal extracts produced vascular effects in the test rat identical with those induced by the blood-borne VEM. Corroboratory evidence for the renal origin of VEM was provided by the absence of VEM in the blood stream in experimental hemorrhagic and traumatic shock induced after exclusion of the kidneys from the circulation.

Similar extracts of tissues of animals allowed to pass into the decompensatory, hyporeactive stage of shock, as determined by the presence of VDM in the blood, showed that the tissue origins of VDM were restricted to the liver, spleen and skeletal muscle. The liver was quantitatively the most significant source of this principle. The amount in skeletal muscle was smaller, particularly in hemorrhagic shock, its concentrations being proportional to the duration of the limb ischemia. In traumatic shock which followed the application of



	Control (B.P. 100-120)	Stage of shock: Hyper-reactive (B.P. 60-70)	Stage of shock: Hypo-reactive (B.P. 40-45)
VDM:VEM ratio in blood	Equal	VEM predominates	VDM predominates
Vaso-constriction	Partial	Marked	Extreme
Vasomotion	Present	Enhanced	Absent
Epinephrine reactivity	1:2 to 1:6 million	Enhanced	Depressed
Capillary circulation	Intermittent	Ischemic, restricted	Sluggish; all vessels open
Venular flow	Rapid, plethoric	Slowed, ischemic	Almost static

FIG. 1. Diagrammatic representation of the circulation in the terminal vascular bed of the omentum and mesentery in the normal state, and during the hyperreactive (VEM predominates) and hyporeactive (VDM predominates) stages of experimental shock. (Reprinted from SHORR, ZWEIFACH, FURCHGOTT and BAEZ. *Tr. A. Am. Phys.*, vol. 60, 1947.) (After Zweifach and Chambers.)

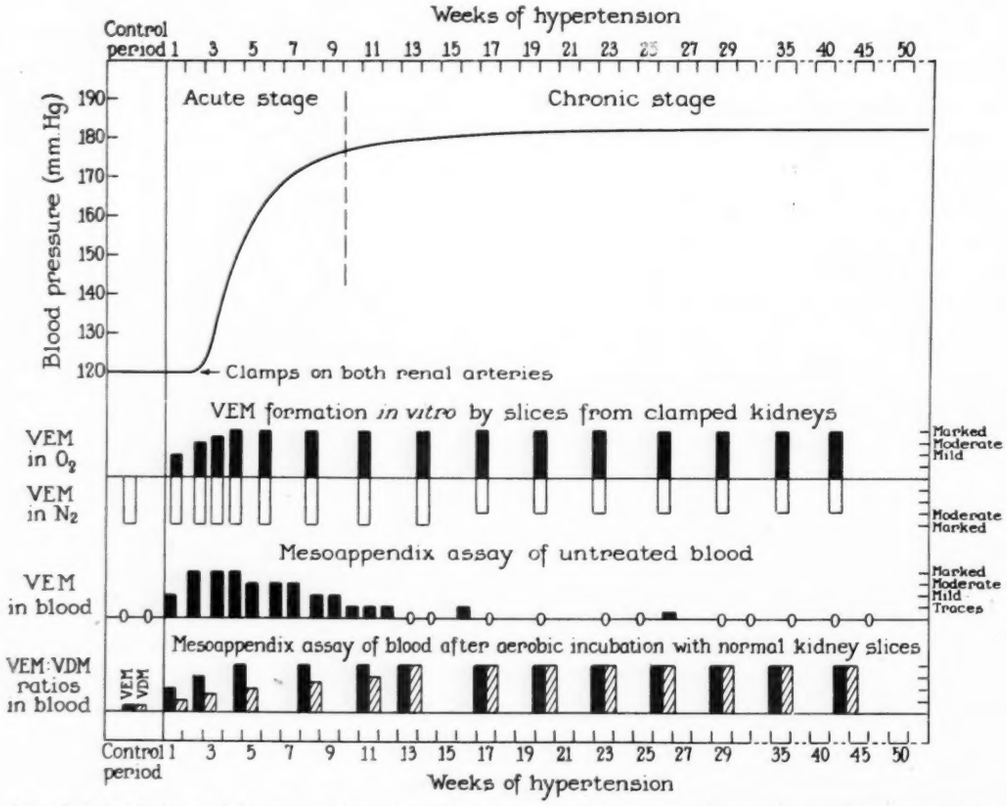


FIG. 2. Metabolic and humoral alterations in hepatorenal vasotropic factors in renal hypertension. (Reprinted from SHORR, ZWEIFACH, FURCHGOTT and BAEZ. *Tr. A. Am. Phys.*, vol. 60, 1947.)

tourniquets for six to ten hours, high concentrations of VDM were present in the saline washes of the muscles from the occluded limbs. It should be stressed that the formation of VDM by the liver was not related to hypotension *per se* but was uniformly confined to the decompensatory phase of the syndrome.

Mode of Origin of VEM and VDM. Having determined the tissues of origin, the next problem was to establish the mode of production of these vasotropic substances. In view of the difficulties presented in interpreting results in the living animal, *in vitro* procedures were employed by which specific environmental factors could be varied. Since tissue hypoxia prevails during shock, the influence of this environmental condition was first investigated. The same variety of tissues as well as brain cortex was obtained from normal animals and prepared as for microrespiration experiments. The tissues were then exposed to anaerobiosis *in vitro* for periods of two hours or longer in a Ringer phosphate or Krebs' bicarbonate medium. Control experiments were carried out under aerobic conditions. None of these tissues produced either VDM or VEM under aerobic conditions; under anaerobic conditions VDM was formed by the same tissues from which it was found to originate in the living animal, namely, liver, skeletal muscle and spleen. Only one tissue, renal cortex, was found to produce VEM anaerobically.

Inactivation of VEM and VDM. The third aspect of these studies was related to the persistence of VDM in the blood stream during irreversible shock despite transfusions, as contrasted with its rapid disappearance after injection into the normal test rat. It seemed probable that mechanisms existed in the healthy animal for the removal of this factor whereas the animal in irreversible shock had lost this property. This question was likewise studied by *in vitro* procedures. These consisted in the exposure of a variety of tissues from normal animals to VDM under aerobic conditions for a period of two hours. It was found that only the liver possessed a mechanism for inactivating VDM oxidatively. This finding led to an investigation of the possibility that mechanisms might also exist for the aerobic inactivation of VEM. Such a mechanism was found to exist in the renal cortex and to a smaller extent in the liver.

It was also observed that the VDM inactivating mechanism in the liver was progressively damaged by prior exposure of the liver to anaerobic conditions. Upon restoration of oxidative conditions after two hours of anaerobic incubation a marked deterioration of the VDM inactivating capacity of the liver was regularly observed. A similar depression of the capacity to inactivate VDM was characteristic of the liver during the decompensatory, irreversible stage of shock, an observation which appears to provide an explanation for the persistence of VDM in the blood in irreversible shock despite the temporary restoration of oxidative conditions by transfusions. This is believed to comprise a crucial defect since the body can no longer liberate the vascular bed from the decompensatory action of VDM. During the compensatory phase, when the animal remains recoverable by transfusion, the VDM inactivation capacity of the liver was found to be unimpaired.

These observations have provided a basis for a concept of shock which can be briefly summarized as follows: The initial reaction to blood loss involves a reduction in renal blood flow sufficient to initiate anaerobic processes in the kidney which lead to the formation of VEM. This principle predominates in the blood stream and leads to the development of a type of vascular hyperreactivity favorable to the maintenance of an adequate circulation in the face of reduced blood volume. During this phase of shock, in which the renal vasoexcitor dominates vascular behavior, the animal is recoverable by transfusion. If, however, the shock is prolonged and hypotension profound, the renal blood flow is virtually abolished and there is no further release of VEM into the blood stream. The reduction in blood flow to the liver is now sufficient

to initiate anaerobic processes in that organ. These lead to the formation of VDM and its release into the blood stream in amounts eventually sufficient to dominate the behavior of the terminal vascular bed. The vascular effects of VDM are decompensatory in character and make for progressive reduction in the effective blood volume with terminal peripheral failure. Once this stage is well established, transfusions are of temporary benefit since VDM will continue to dominate vascular behavior because of the damage sustained by the liver VDM inactivating system as a result of the previous hepatic anoxia. Considerations of space have permitted only a very brief and incomplete description of our experiments dealing with the participation of VEM and VDM in experimental and traumatic shock. For a more detailed account the reader is referred to other publications from this laboratory.[6,7]

Before considering the participation of these vasotropic principles in experimental renal hypertension we may recapitulate the characteristics of these two oppositely acting principles and the systems which govern their formation. The formation of both VEM and VDM *in vitro* is limited in a normal kidney and liver to states of reduced oxygen tension. Under aerobic conditions VDM is inactivated by the normal liver, VEM by the normal kidney. These phenomena represent a type of Pasteur reaction analogous to the limitation of lactic acid formation by the normal tissue to anaerobiosis and to its disappearance by oxidation or storage under aerobic conditions. The VEM-forming and inactivating mechanisms are restricted to the renal cortex. It has not yet been possible to determine which type of liver cell is involved in VDM formation and inactivation. VDM and VEM exert diametrically opposite effects on the terminal vascular bed. VEM enhances the reactivity to epinephrine and increases vasomotion of the metarterioles and precapillaries; by augmenting the constrictor phase of the vasomotion of the precapillaries it serves to restrict the blood flow through the true capillary bed. VDM, on the other hand, reduces the epinephrine reactivity of the metarterioles and precapillaries, depresses vasomotion and by prolonging the dilator phase of the precapillary sphincters, favors the filling of the capillary bed. These opposite vascular effects have led us to postulate that these vasotropic principles may represent components of opposite action in a homeostatic system participating in the regulation of peripheral blood flow. In the blood stream of the normal animal, these principles apparently exist in an equilibrium at low concentrations, blood from such animals giving a neutral reaction in the rat meso-appendix test. In the course of development and progression of the shock syndrome this equilibrium is shifted first in one and then in the other direction. During the initial compensatory phase there is a preponderance of VEM associated with vascular hyper-reactivity. During the subsequent decompensatory stage VDM preponderates with the resultant development of hyporeactivity. Preponderance of one or the other of these vasotropic principles is an expression of the reaction of the organism to a type of stress requiring profound vascular readjustments, namely, a reduction in effective blood volume, and is a reflection of the effects of reduced oxygen tensions on specific metabolic processes in the kidney and liver. Our findings as to the participation of VEM and VDM in the syndrome of experimental renal hypertension can now be projected against this background.

Vasotropic Content of Blood during Acute and Chronic Renal Hypertension.[2] Dogs were made hypertensive by the application of Goldblatt clamps to the renal arteries. Prior to the application of the Goldblatt clamp, 0.5 cc. of heparinized whole blood gave a neutral reaction when injected into the normal rat for bio-assay by the meso-appendix technic. Within thirty minutes of the partial constriction of the renal artery VEM appeared in the renal vein blood and a few hours thereafter could be detected in the peripheral blood. Blood from such dogs continued to show pronounced VEM activity during the period in which the blood pres-

sure was progressively rising. VEM disappeared from the blood when the blood pressure had become stabilized in the hypertensive range in dogs with two renal clamps, or with one kidney clamped and the other removed, or when the blood pressure had fallen to normal levels in dogs with one kidney clamped and the other intact. In the last group clamping of the second kidney resulted in the reappearance of VEM during the subsequent rise in blood pressure; on stabilization of the blood pressure at new hypertensive levels VEM again disappeared from the blood stream.

Evidently the partial constriction of the renal artery by the Goldblatt clamp rapidly led to the release of VEM by the clamped kidney and to its predominance in the blood stream throughout the stage of acute hypertension. Once the blood pressure had stabilized at the hypertensive level this preponderance disappeared, the blood again giving a neutral reaction. On the basis of our *in vitro* studies of the mechanism of VEM formation it seemed probable that the appearance of VEM in the blood stream was related to the temporary renal hypoxia resulting from the clamping of the renal artery. The return of a neutral reaction of the blood at chronic hypertensive levels might be attributed to restoration of a more adequate blood flow at these higher levels of blood pressure. Our next group of experiments were designed to test the validity of these hypotheses.

VEM Mechanisms in the Clamped Kidney of the Hypertensive Dog.[3] It will be recalled that *in vitro* studies showed that VEM production by the healthy kidney took place olny under anaerobic conditions, the kidney slice forming none in oxygen and actually inactivating VEM under aerobic conditions. Similar studies were now carried out on kidneys removed at intervals after the partial constriction of the renal artery by a Goldblatt clamp with the induction of hypertension. Within five and one-half hours and for as long as forty-five weeks after the partial occlusion of the renal artery, the kidney was found to have undergone transformation into an organ which now elaborated VEM continuously even on aerobic incubation. This situation is comparable to the derangement of the glycolytic mechanism in cancer cells by which lactic acid is formed in both oxygen and nitrogen. Studies of clamped kidneys removed at all stages in the hypertensive syndrome showed a persistence of this metabolic defect even in those animals with only one kidney clamped and whose blood pressure had returned to normal. The clamped kidneys also exhibited a progressive impairment of their capacity to inactivate renal VEM on aerobic incubation *in vitro*. The basis for the aerobic production of VEM by clamped kidneys of hypertensive dogs would appear to reside in the loss of the renal mechanism for inactivation of VEM. As a consequence the homeostatic mechanism within the cell, by means of which VEM formation can be regulated, becomes deranged so that VEM is formed continuously under conditions which would ordinarily check its formation. Although the initial damage to the VEM inactivating system would appear to have its explanation in the reduced oxygen tension which follows the application of the clamped kidney, there appears to be no present explanation for the persistence of this defect during the stage of chronic hypertension when the blood pressure has risen to a level which is sufficient to maintain an adequate blood flow through the kidney as judged by the maintenance of its excretory function. Studies of the oxygen consumption of the kidney at intervals as long as forty-five weeks after the application of the clamps have shown the oxygen consumption to remain within the normal range, suggesting that the blood supply to the kidney has been adequate for its oxidative requirements.

We have also investigated the time relationship of the transformation of this "Pasteur reaction" by which a normally anaerobic process occurs under aerobic conditions. This was done by observing the effects of acute renal ischemia on the *in vivo* and *in vitro* formation of VEM.[8] Occlusion of the renal circulation in rats for ten to

twenty minutes was followed by a transient hyper-reactivity to epinephrine of the terminal blood vessels in the meso-appendix. With more prolonged renal ischemia (twenty to ninety minutes), persistent hyper-reactivity developed, the vessels becoming 20 to 200 times more responsive to epinephrine for at least sixty minutes, the period of observation. With renal ischemia lasting 150 to 240 minutes, a gradual deterioration of the VEM mechanism occurred, little or no vascular hyper-reactivity resulting.

The *in vivo* changes were shown to be related to specific alterations in the mechanisms for VEM formation and inactivation by means of *in vitro* incubation studies of ischemic kidneys. Kidney slices ischemic for ten to thirty minutes before incubation resembled a normal kidney, forming VEM only anaerobically. After forty to ninety minutes of ischemia, kidney slices produced VEM even under aerobic conditions. With more prolonged ischemia (120 minutes or longer), there was a progressive impairment in the ability of the kidney to form VEM both aerobically and anaerobically, as well as a deterioration of the renal mechanism for VEM inactivation. These experiments appear to be relevant to the findings with the clamped kidneys of hypertensive dogs and would suggest that the initial period of renal hypoxia following partial occlusion of the renal artery may be responsible for the alteration in the renal VEM mechanism whereby VEM is formed both aerobically and anaerobically. They provide no explanation, however, for the persistence of this metabolic defect in the clamped kidney during the period in which the blood flow has become adequate as a result of the hypertension.

Vasotropic Content of "Neutral" Blood during the stage of Chronic Hypertension.[1] The possibility was explored that the actual concentrations of VEM were high in the blood but that they were neutralized by equivalent amounts of VDM. Such a state might be anticipated if the renal and hepatic principles were counterparts of a homeostatic system. Exploration of this hypothesis was accomplished by utilizing the ability of healthy kidney tissue to inactivate VEM *in vitro* under aerobic conditions without a comparable inactivation of VDM. The inactivation of VEM by aerobic incubation of blood with normal kidney slices would thereby unmask any VDM which was present and permit its detection. When this procedure was carried out with bloods of normal animals, no VDM could be detected by the rat meso-appendix test. When, however, "neutral" blood from dogs in chronic hypertension was similarly treated, large amounts of VDM were invariably revealed, suggesting that a new equilibrium had been established with higher concentrations of both factors. It is of interest that the new equilibrium level is generally achieved at about the time the blood pressure is being stabilized at a new hypertensive level.

Similar studies were carried out on the blood of twelve subjects with essential hypertension, using normal healthy adults as controls. The results were identical with the findings in normal dogs and those with chronic renal hypertension. Prior to aerobic incubation with normal kidney slices, bloods from normal controls were neutral; those from the hypertensive patients were either neutral or produced a slight vasoexcitor effect in the test rat. Following incubation, bloods from the normal subjects remained neutral whereas those from the chronic hypertensives induced a profound VDM effect in the test rat. These findings establish another point of similarity between experimental renal hypertension and essential hypertension in man.

Relation of the Adrenals to Formation of VEM.[9] The necessity of intact adrenal cortical function for the maintenance of experimental hypertension and the hypotension which invariably follows adrenalectomy in normal animals, prompted an investigation of the state of the renal VEM mechanism following adrenalectomy. At various intervals after adrenalectomy in rats, rabbits and dogs the capacity of the kidney to form VEM under anaerobiosis was

studied *in vitro*. Three procedures were employed: (1) adrenalectomy; (2) adrenalectomy plus a high sodium chloride intake and (3) adrenalectomy plus sodium chloride and desoxycorticosterone (0.1 mg./Kg. daily). The renal capacity to form VEM under anaerobic conditions *in vitro* was found to become progressively impaired and in most instances was completely abolished even in animals maintained on high salt intakes. However, kidneys removed from adrenalectomized animals maintained on desoxycorticosterone acetate and salt for ten to fifteen days postoperatively, behaved like normal kidneys with respect to VEM formation. Observations were also made on the mesenteric blood vessels of adrenalectomized rats during the development of the syndrome. As adrenal insufficiency developed the vessels exhibited a progressive unresponsiveness to epinephrine as well as a progressive inability to respond to the intravenous administration of VEM. These experiments appear to establish the necessity of an intact adrenal cortical mechanism for the proper functioning of the renal VEM mechanism.

SUMMARY

We are now in a position to attempt a synthesis of the evidence for the participation of hepatorenal vasotropic factors in experimental renal hypertension. Shortly after the partial constriction of the renal artery by a Goldblatt clamp, significant amounts of VEM appear first in the renal vein blood and then in the peripheral circulation. The mechanism responsible for this shift in humoral equilibrium appears to be a specific alteration in renal metabolism as a result of which VEM is formed aerobically as well as anaerobically. This situation is indicative of a breakdown of the normal intracellular homeostatic mechanism by which *in vitro* VEM formation can be regulated by variations in oxygen tension. Acute *in vivo* and *in vitro* experiments suggest that this derangement is brought about by the period of hypoxia attendant upon the initial reduction of renal blood flow which follows application of the clamp.

This defect in the renal VEM mechanism of the clamped kidney persists throughout the syndrome. Nevertheless, a preponderance of humoral VEM prevails only during the period of rising blood pressure. When the blood pressure has been stabilized at hypertensive levels, presumably with the restoration of an adequate renal blood flow, the blood again becomes "neutral." This neutrality is due to the appearance in the blood stream of increasing amounts of VDM which eventually reach a concentration adequate to neutralize the heightened concentration of VEM. The neutral state therefore represents the establishment of a new equilibrium between VEM and VDM at greatly augmented concentrations of both factors. A similar situation exists in the blood of patients with essential hypertension. The reasons for the persistence of the hypertensive state when the blood has again become neutral remains a matter for further study. The persistence of this defect in the renal VEM mechanism in dogs with one kidney clamped and the other intact and in whom the blood pressure has returned to normal, suggests that the unclamped hypertrophied kidney is inactivating the excess VEM which is continuously elaborated by the clamped kidney. A relation of the above phenomena to the adrenal cortex was brought out by experiments which showed that kidneys from adrenalectomized animals could no longer form VEM *in vitro*. Desoxycorticosterone, but not NaCl, restores this mechanism to the kidney of the adrenalectomized animal.

COMMENTS

At the present stage of this study we would prefer to limit a consideration of these observations to the descriptive level and to place emphasis on the regularity with which these vasotropic principles appear in the blood and the uniformity with which specific derangements develop in the renal VEM mechanisms during experimental renal hypertension. That a causal relationship exists

between these derangements and the development of renal hypertension cannot be definitely established on the basis of present data.

It should be pointed out that during the acute stage of renal hypertension the blood contains not only an excess of VEM but increased amounts of renin and hypertensin (angiotonin) as well. The question therefore arises whether or not VEM constitutes a distinct entity apart from renin and hypertensin. Some information has been obtained that this is the case.[10] Its differentiation from renin, *per se*, is evident from its heat stability and the fact that it is dialyzable. Involvement of renin in VEM elaboration by the kidney cell remains uncertain. Thus, the unclamped hypertrophied kidney of the dog in which transient hypertension has been induced by clamping one renal artery, has been found to be devoid of renin.[11] Nevertheless, we have found that such kidneys form VEM under anaerobic conditions *in vitro*. The kidney of the adrenalectomized dog was noted by Goldblatt to have a normal renin content.[12] Such kidneys do not form VEM anaerobically even when incubated with normal plasma containing an abundance of renin substrate.[9] It is conceivable, however, that the failure of VEM formation under these circumstances might be due to the absence of an appropriate intracellular substrate.

The differentiation of VEM from hypertensin is more difficult. Not only are both heat stable and dialyzable, but the kidney extracts containing renin, by means of which hypertensin is prepared *in vitro*, are almost invariably contaminated with VEM which is not destroyed during the preparation of hypertensin. We have, however, observed no correlation between the pressor activity, which is the essential action of hypertensin, and the VEM activity of such hypertensin preparations. This would suggest that whatever VEM activity is exhibited by these preparations is due to the initial contamination of the renin extracts with VEM. Experiments on isolated smooth muscle preparations have established the musculotropic effect of hypertensin. Concentrated VEM preparations much stronger than those required to elicit epinephrine reactivity in the test rat are devoid of musculotropic effects.[10] It has also been possible to dissociate VEM from hypertensin or hypertensin-like substances by occlusion of the renal circulation for long periods, e.g., four hours or longer, and its subsequent release.[13] Although kidneys damaged by this procedure have lost the capacity to form VEM, they discharge material into the circulation with a distinct pressor effect attributed to hypertensin by Taquini.[14] There are other differentiating features: In contradistinction to hypertensin, which is formed by the interaction of renin on an α_2 globulin in the blood, VEM is the product of intracellular metabolism. It is formed by renal cortical tissue, washed free of all blood and incubated in Ringer phosphate or Krebs' bicarbonate medium. Of particular significance is the circumstance that VEM appears to influence chiefly that part of the vascular bed distal to those arterioles on which hypertensin exerts its constrictor effect. Finally, the persistence of VEM in the blood stream during the chronic phase of hypertension contrasts with the disappearance of detectable amounts of renin and hypertensin in that stage of renal hypertension.

Several points concerning the action of VEM should be emphasized: First, the fact that this vasoexcitor principle is assayed by its potentiating effect on the constrictor response to epinephrine does not imply that the rôle of VEM in the organism consists in the potentiation of epinephrine. It is more likely that the vascular response to topically applied epinephrine represents a reaction more closely allied to the local reaction of the neuromuscular effector unit to a naturally occurring substance such as sympathin. Nor does the potentiation of the local responce to topical epinephrine necessarily imply a corresponding change in the pressor response of the vascular system to intravenously administered epinephrine.

Second, the terminal vascular unit under consideration constitutes a unique segment

of the vascular tree which is under the dual influence of both systemic and local tissue factors; the metarterioles and precapillaries are the components most highly responsive to humoral substances. The primary functions of these vessels are concerned with the peripheral distribution of the blood and, through the process of vasomotion, with the adjustment of the pressure and volume of flow in the capillary bed relative to that in the feeding arterioles. Thus, the vasoexcitor principle, VEM, acts for the most part on a component of the vascular tree which is not directly concerned with the regulation of peripheral resistance and blood pressure. In this respect, VEM differs from the pressor agents, such as hypertensin, which act on the larger arterioles and which effect *acute* changes in blood pressure by their constrictor effects on these vessels. The potential effect of VEM on peripheral resistance and blood pressure would therefore have to be of an indirect and chronic character. What is suggested as a possible mechanism is the initial development, under the influence of VEM, of a sustained state of hyper-reactivity in the terminal metarterioles and precapillaries, a condition which we have observed to occur in the rat during the stage of acute hypertension.[15] The persistence of such a state of hyper-reactivity would, in time, of necessity lead to the development of a tonically constricted state in the larger arterioles. This could come about either via a humoral mechanism or through a local axon type of reflex such as is normally responsible for arteriolar changes in response to changes in the capillary bed. Our studies are now being directed toward the exploration of these concepts.

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Conference on Therapy

Uses of Streptomycin

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. HARRY GOLD: The use of streptomycin is the topic of the conference today and the opening remarks will be made by Dr. Walsh McDermott.

DR. WALSH MCDERMOTT: It was about three years ago that Dr. Waksman and his associates reported the discovery of the antibacterial agent, streptomycin. They not only discovered that the drug was effective *in vitro* against a number of gram-negative bacilli and the tubercle bacilli but also demonstrated that the drug was effective in certain experimental infections in animals. Within a year, Drs. Hinshaw and Feldman at the Mayo Clinic reported that streptomycin exerted a suppressive effect on the course of tuberculosis in guinea pigs and, soon thereafter, started their now well known studies of the effects of streptomycin in tuberculosis in humans.

The evaluation of the clinical effectiveness of streptomycin in infections other than tuberculosis has proceeded rapidly. In two successive issues of the Journal of the American Medical Association (132: 4, September 7th and 132: 70, September 14, 1946), the Committee on Chemotherapeutics headed by Dr. Keefer reported the results with streptomycin in 1,000 patients with various types of non-tuberculous infections. This report also contains information on the pharmacology and other fundamental aspects of the drug. Since this report is readily available, I shall endeavor to avoid duplicating its material.

Later we shall consider the use of streptomycin in tuberculosis separately. In other clinical conditions, results with streptomycin have been most satisfactory in four types of infections: First, urinary tract infections caused by Escherichia coli or the other gram-negative bacteria which frequently produce infections of the urinary tract such as Bacillus lactis aerogenes, Bacillus proteus, Friedländer's bacillus and, in some instances, Bacillus pyocyaneus; second, meningitis caused by Hemophilus influenzae; third, tularemia and fourth, a miscellaneous group of infections, pneumonias, abscesses, peritonitis and the like caused by the same group of gram-negative bacteria which frequently produce urinary tract infections.

Equivocal results have been observed in acute brucellosis and in acute systemic infections due to food poisoning caused by the Salmonella group. The results in typhoid fever have been disappointing and it is impossible, at this time, to state with any degree of certainty whether streptomycin exerts any effect on the course of the typhoid infection in humans.

In the four types of infection in which streptomycin is of unquestioned effectiveness, the results have generally been as prompt and, in many instances, as dramatic as we have been accustomed to see following the use of penicillin in pneumococcus pneumonia. One of the greatest sources of difficulty in the use of streptomycin is the development by bacteria of resistance to streptomycin. This happens with more regularity and greater speed than in the case of other antibacterial agents. As a result, the total period during which the

drug may be used effectively is limited. In the treatment of infections in the urinary tract, in which there is no appreciable degree of anatomic damage or obstruction which cannot be removed, the control of the infection by streptomycin may be obtained fairly quickly before the development of bacterial resistance. However, if permanent anatomic damage is present so that it is impossible to eradicate the infection completely, the administration of streptomycin may be followed by a remission and then by a relapse due to streptomycin-resistant organisms. The same general principle holds for all types of streptomycin-sensitive infections, including tuberculosis. Dr. Finland has made the interesting observation that, in urinary tract infection, the development of resistance to streptomycin by the gram-negative bacilli is appreciably reduced, if not eliminated, by maintaining the urine in a neutral or alkaline state.

Streptomycin should be used in the treatment of Hemophilus influenzae meningitis although an alternate type of effective therapy is available. In the treatment of Hemophilus influenzae meningitis, it must again be borne in mind that resistance may develop rapidly and one should be quick to utilize the alternate method of treatment in patients in whom streptomycin does not seem to be effective. In Friedländer's pneumonia, there is a rapidly necrotizing infection caused by an organism which is susceptible to both streptomycin and the sulfonamides. There is theoretical evidence to support the notion that the simultaneous administration of two active drugs might greatly diminish the chance of the development of resistance to either drug. Thus, it would seem to be wise at this time to use sulfadiazine as well as streptomycin in all of these cases.

It may prove worth while to give streptomycin a trial in instances of Salmonella infection in which bacteremia is present but whether an effect is to be anticipated cannot be said at this time.

We may summarize the situation with regard to the non-tuberculous infections as follows: Streptomycin is a potent agent for the treatment of Escherichia coli infections and it is the only available antimicrobial agent for the treatment of infections due to several other gram-negative bacteria. It should therefore be used in serious urinary tract infections due to Escherichia coli, in other types of urinary tract infections caused by Bacillus lactis aerogenes, Bacillus proteus, Friedländer's bacillus and Bacillus pyocyaneus. It should also be used in the treatment of peritonitis from appendiceal or diverticular ruptures because this type of peritonitis is frequently caused by streptomycin-sensitive organisms. It is effective, and should be used, in the treatment of Hemophilus influenzae infections. It is as yet of undetermined and probably questionable value in infections due to Salmonella and the Bacillus typhosus.

More than a year ago, Dr. Muschenheim, myself and our associates began our studies on the effects of streptomycin in human tuberculosis. This was prompted by the reports of Dr. Hinshaw and Dr. Feldman who noted that the administration of streptomycin produced a marked effect on the course of various types of tuberculous infections in man. Drs. Hinshaw and Feldman were very restrained in the conclusions which they drew from their observations but it was obvious from the data presented by them that their results with tuberculosis were unprecedented. Our own results have constituted a complete confirmation of their reports.

Up until now we have treated about forty-five patients with various types of tuberculosis. In general, three types of notable phenomena were observed in this group of patients: First, in the patients who were acutely ill, there was an abrupt or at least a rapid defervescence with accompanying symptomatic improvement. In some patients, the defervescence was as dramatic as the crisis of pneumococcus pneumonia. Second, in many of the patients there was a marked regression of the lesion. At times this regression continued to the

point of complete disappearance of the lesions demonstrable by x-ray. That specifically has occurred in patients with acute miliary tuberculosis. The third phenomenon was the development of bacterial resistance.

While the most dramatic results were observed in patients with acute hematogenous tuberculosis, it is not to be anticipated that generally favorable results will frequently be obtained in this condition. There are three reasons for this: The first is the high incidence of meningitis as a complication of acute miliary tuberculosis. Meningitis may be present either at the start of therapy or make its appearance during the second or third month. Secondly, relapsing miliary tuberculosis is to be anticipated and the third reason is one already indicated for other infections, namely, the development of resistance to streptomycin.

In meningitis without miliary tuberculosis, the situation is about the same as in the case of miliary tuberculosis. I would hazard the guess, on the basis of Dr. Hinshaw's experience, our own experience, the experience in the Veterans' Administration program and from the results in a few scattered patients treated here and there, that between one-fifth to one-tenth of patients with tuberculous meningitis will attain an eventually satisfactory result following the use of streptomycin.

Long-standing pulmonary tuberculosis, with cavitation and much fibrosis, has not, thus far, been appreciably benefitted by the administration of streptomycin. The surrounding infiltration may regress. The patient may feel better during this phase of the therapy. However, in every patient thus far, streptomycin-resistant strains of organisms have developed.

The form of tuberculosis in which the most satisfactory results have been observed has been the exudative disease of short duration with moderately advanced or even far advanced lesions. Here presumably there are no anatomic barriers to rapid arrest of the lesion. In this stage of the disease, effective antimicrobial therapy for six or eight weeks may well spell the difference between success or failure. From the studies we have made on the resistance of the tubercle bacilli to streptomycin it seems that in the majority of patients resistance appears between the fourth and eighth week of therapy. Therefore, effective therapy with streptomycin is limited to a great extent to those types of tuberculosis in which it is possible to obtain a significant reversal of the course of the disease within a period of four to eight weeks. Exudative disease, with or without thin-walled cavities, is the type of pulmonary tuberculosis in which it is conceivable that this could happen and from our experience thus far it seems that it does happen.

Just one more point on tuberculosis. I think we have clear cut preliminary evidence that the development of streptomycin-resistance by the tubercle bacillus, demonstrable *in vitro*, is paralleled by clinical evidence of this resistance *in vivo*. Of the first eleven patients who developed bacterial resistance demonstrated *in vitro*, eight developed clinical relapses during therapy and in five of the eight, the relapses progressed to a fatal termination despite the fact that streptomycin therapy was continued. In each instance, the relapses occurred after a period of dramatic improvement. Therefore, I believe there can be no question but that the development of streptomycin resistance, demonstrable by *in vitro* tests, means that the usefulness of the drug in that particular infection has come to an end. I should like to point out that the development of drug resistance by organisms in the central nervous system may, however, proceed at an entirely different rate from that in those patients with infections of the lung.

Unlike penicillin, streptomycin has important toxic properties. Four types of toxic reaction have been observed: The first is the so-called histamine reaction, which does not occur with the presently available material and, therefore, no longer gives any concern.

The second type consists of various manifestations of delayed anaphylaxis or sensitivity reactions. These reactions are identical with drug fevers and rashes which are observed after the use of any number of drugs. When one encounters such a reaction, it is advisable to re-evaluate the need for therapy. Fortunately, in many cases of non-tuberculous infections, by the time the reaction appears the need for drug therapy is over and one can discontinue the use of streptomycin without endangering the patient. In tuberculosis, on the other hand, that is not the case and in such instances one must decide whether the tuberculosis or the sensitivity reaction carries the greater threat to the patient. Eosinophilia is another type of sensitivity reaction due to streptomycin. The eosinophilia is usually marked and may represent as much as 35 to 40 per cent of the white cell count. In one instance in our series, it was accompanied by tenosynovitis. No evidence of peripheral vascular disease has been noted thus far although eosinophilia of that degree has caused us some apprehension.

The third type of reaction, that of renal irritation, is evidenced largely by granular casts. This may be prevented by maintaining urine on an alkaline basis. It is difficult to establish whether normal kidneys are permanently damaged by this process. I think the evidence is highly suggestive, however, that kidneys previously damaged by other disease can be further damaged by streptomycin. Beyond doubt, renal insufficiency appears and progresses under the administration of streptomycin. This has now been noted by many observers. It is well, therefore, to be extremely cautious in the administration of streptomycin to any patient with known renal disease.

The fourth type of reaction constitutes the only serious drawback to the use of the drug from the standpoint of toxicity. It is a central nervous system reaction characterized by vestibular dysfunction and occasionally accompanied by deafness. Evidence of this type of reaction appears in all patients who receive 2 or more Gm. of streptomycin daily for longer than three or four weeks. The reaction usually starts as a mild headache which gathers intensity within twenty-four hours and then disappears. The vestibular disorder then appears. It is not a true vertigo as a rotary component is lacking. There is however a very definite sensation of overshooting the mark; for example, in initiating a movement in any direction, the patients have the sensation that the movement is continuing after it has actually stopped. As a result, they may believe they are falling to one side or the other, or forward and may be acutely uncomfortable. There is considerable variation in the intensity of this reaction. In some patients, perhaps one-third, it is negligible and the symptoms can be elicited only on careful questioning. In another third, the symptoms are moderately acute for a period of a week or ten days and then subside almost, but not quite, completely. In the remaining third, or in perhaps a somewhat smaller number, the symptoms are much more severe and last longer. These patients are unable to sit erect in bed or move about with their eyes open but after these symptoms subside minimal vestibular dysfunction may persist for as long as sixty days and in some, they appear to persist indefinitely. Recovery from this vestibular dysfunction seems to occur by virtue of compensatory mechanisms and not by restoration of labyrinthine function. In some patients, this type of compensation may never occur or may occur only after many months of dysfunction. Dr. Hinshaw has observed, and it was also noted here and by others, that elderly patients do not effect compensation after the development of the reaction as readily as younger patients. This is a point of great importance to the urologist who is faced with the problem of urinary tract infections in men in their seventies.

Deafness, fortunately, is a rare symptom. In the Mayo Clinic and in the New York Hospital-Cornell series, it has been seen only under three conditions; in those patients who received very large doses of streptomycin, 5 to 10 Gm. daily, in those who

received the drug intrathecally and in patients with renal insufficiency. I should state that 3 Gm. a day, or at most 4 Gm., is the upper limit of safe dosage. Even this may prove toxic in patients with renal damage because of accumulation of the drug. The patients with deafness after intrathecal administration had meningitis and it is difficult to be certain whether the deafness was due to the disease or to the drug but, at least in some instances, it was probably due to the drug. It is safe to say that in patients with normal renal function in whom the drug is given intrathecally, deafness will rarely occur with a daily dose of 3 Gm.

DR. GOLD: The subject is now open for discussion. Are there any questions?

INTERN: In a recent issue of the Journal of Venereal Disease Information, there was a report of the use of streptomycin in specific and non-specific urethritis. I believe Dr. Koteen has used streptomycin in gonorrhea caused by organisms resistant to a sulfonamide and penicillin. I wonder if we could hear from him and Dr. McDermott on its use in such cases.

DR. GOLD: How about it, Dr. Koteen?

DR. HERBERT KOTEEN: Dr. Gold, I had the opportunity of using streptomycin in two patients who had penicillin- and sulfonamide-resistant gonococcus infections of the urethra. In one, a woman, there were thirty-two positive cultures during a course of treatment with sulfadiazine and/or penicillin. Thirty-six hours after streptomycin was used, the cultures became negative and remained so. The other patient was a young man who took sulfadiazine on and off for nine months and had five courses of penicillin. His cultures also became negative after 3 Gm. of streptomycin. Two other patients were treated with streptomycin. Both had an Aerogenes infection; in one, it was complicated by Streptococcus alpha and in the other, by a staphylococcus. Both had failed to respond to sulfadiazine and penicillin but responded to combined penicillin-streptomycin therapy. All of these patients received a dose of 2 Gm. of streptomycin daily for five days.

DR. GOLD: Dr. McDermott, did you have a comment?

DR. MCDERMOTT: In summarizing the material so briefly, I omitted mention of certain types of infections by gram-positive organisms against which streptomycin is effective. One very important instance is bacterial endocarditis caused by organisms with a relatively high penicillin-resistance, such as those of the Zymogenes-faecalis group and another is staphylococcus endocarditis caused by penicillin-resistant strains.

VISITOR: I would like to ask Dr. McDermott if he has had any experience with streptomycin in typhoid carriers and whether he ever used it orally in an attempt to sterilize the stools with respect to the typhoid organism?

DR. MCDERMOTT: We have no experience along those lines. We have treated only six patients with typhoid fever. They were all early cases and were excellent for clinical evaluation since all had bacteremia at the time treatment was started. In four, there was no effect. Two patients did very nicely in terms of the progress of their typhoid fever but we do not know whether the favorable course was related to the streptomycin. It would be my guess that streptomycin would have only a temporary effect on the carrier state and that this would not persist after the streptomycin was discontinued.

DR. MCKEEN CATTELL: I would like to ask Dr. McDermott whether we may not anticipate that, if streptomycin is widely used in the treatment of tuberculosis, most infections will eventually be of resistant strains?

DR. MCDERMOTT: Dr. Cattell, I think we can almost guarantee it, if enough tuberculosis is treated with streptomycin. We do not know, of course, how long the strains remain streptomycin-resistant after the drug is discontinued. Thus far, the few which we have treated have remained resistant for as long as ninety days following a four-month period of therapy. However, it may be that in six months or so they revert to their original state of streptomycin-sensitivity.

I believe, and I am sure Dr. Muschenheim agrees with me, that the importance of streptomycin in tuberculosis lies not so much in its own potential for the cure of tuberculosis, as in the demonstration, by means of this drug, that it is possible to affect the course of the tuberculous infection with a chemotherapeutic agent. We hope that eventually there will be a better agent than streptomycin for the long pull in this disease.

DR. GOLD: Dr. McDermott, is there a record of a single patient with tuberculosis who has been cured by streptomycin?

DR. MCDERMOTT: Oh, yes, I would say that of Dr. Hinshaw's patients with meningitis. Would you go along with that, Dr. Muschenheim?

DR. CARL MUSCHENHEIM: Those patients have been followed for six months or more but whether they could be called "cured," I think, is somewhat doubtful. I do not think that there has been any more evidence that tuberculosis is "cured" by streptomycin than that it is "cured" by any other method of treatment. I am talking about tuberculosis in general. I think that we still must speak in terms of "arrest" and that we still must expect relapses on the same basis and caused by the same influences as we have found in the past with other forms of treatment.

DR. MCDERMOTT: The term "cure" should not be used. The action of streptomycin was originally described by Hinshaw and Feldman as "suppressive." Actually, all antimicrobial agents are "suppressive." Streptomycin is in no way different in its effect on tuberculosis than any other antimicrobial agent on other infections. What we should anticipate from streptomycin and future antituberculous agents is not a dissolution of all tubercle bacilli within the body, but rather the conversion of all, or nearly all cases, of certain types of active tuberculosis into the equivalent of the best results previously obtained by natural mechanisms.

DR. MUSCHENHEIM: I would like to refer to the statement made by Dr. McDermott that streptomycin is not the ideal drug in the treatment of tuberculosis because of the development of resistance. I do not think that he intended to convey the impression that streptomycin could not be useful in a general program of treatment of all kinds of tuberculosis. He indicated that there are particular phases of tuberculosis, namely, the exudative ones in which the effect of streptomycin is most dramatic.

Another point concerns the fact that the effectiveness in tuberculosis may be of brief duration. Therefore, in applying streptomycin in association with other forms of treatment, such as surgery or collapse therapy of various kinds, we should choose the time very carefully. We do not want to shoot our bolt, so to speak, before we really need it.

DR. WALTER MODELL: This is the first time, I think, that I have heard Dr. McDermott advise the combined use of two chemotherapeutic agents. I wonder, in view of that, what he thinks about using streptomycin together with one of the sulphones, such as promin, which had been recommended some time ago as an effective antitubercular agent.

DR. MCDERMOTT: Implied in your query is the view that the combined use of antimicrobial agents may materially diminish the development of resistance to either agent. There is impressive *in vitro* evidence that it may be so. This has been a subject of a great deal of debate and speculation.

The combined use of streptomycin and promin is now being tried out. It should take a relatively short period of time to find out whether promin is useful when combined with streptomycin because the development of resistance to streptomycin is so uniform.

DR. MORRIS PEARLMUTTER: How should one treat a fulminating case of influenzal meningitis, Dr. McDermott?

DR. MCDERMOTT: I am probably not the one best qualified to answer that since I am not a pediatrician but I will answer it anyway. I would use streptomycin alone for a twenty-four-hour period. At the end of that time, I would be guided principally by the findings in the spinal fluid, especially by the

number of bacteria. They are relatively easy to demonstrate by the quellung test. If it fell from 1,000 to the order of about 20, I would continue the streptomycin but if the effects were not as impressive, I would most certainly switch to Dr. Alexander's immune serum and sulfadiazine. In the few patients whom we have treated, the results have been dramatic with streptomycin alone.

DR. PEARLMUTTER: Suppose the count dropped but slightly, would you then be inclined to treat the patient with all three agents?

DR. MCDERMOTT: I would certainly see no objection to treating with all three or with a combination of two. Sulfadiazine presents no problems. Immune serum is rather expensive and so is streptomycin. I see no theoretical objection, however, to using all three agents together.

DR. GOLD: Dr. Levine, could we have an expression of opinion from you?

DR. SAMUEL Z. LEVINE: In a particularly fulminating case of influenzal meningitis, on the basis of Dr. Alexander's experience, it would seem wise not to postpone the use of the three agents in combination if the response to streptomycin alone were not dramatic. As Dr. McDermott pointed out, it cannot do any harm, except for the cost, and it may do a lot of good.

DR. MCDERMOTT: I did not see Dr. Levine there or I would not have been so presumptuous as to answer that question.

DR. GOLD: Tell us something about the cost.

DR. MCDERMOTT: As a matter of fact, in influenzal meningitis, the expense of streptomycin is not so great because one is usually dealing with an infant or small child. One-half Gm. to 1 Gm., depending upon the size of the child, is usually enough for a daily dose. The market price fluctuates but streptomycin is purchasable at this time for approximately $4.00 for 1 Gm.

VISITOR: What has been the experience with the so-called minimal lesions in tuberculosis?

DR. MUSCHENHEIM: We have not treated minimal lesions although we had one case which was virtually minimal. It was moderately advanced because there was a very tiny cavity. This promptly closed with streptomycin. The patient was a young colored girl who, with a good deal of bed rest, had failed to obtain an arrest of the disease. It was only because the disease has such a serious prognosis in her particular age, sex and race that we even considered treating her with streptomycin.

In general, I believe, and I think Dr. McDermott agrees with me, that minimal cases should not be treated with streptomycin. We know nothing yet about the late toxic sequellae of the drug. Dr. McDermott has called attention to the eosinophilia which causes some concern since it might indicate serious, late sequellae. We hesitate to give streptomycin in these minimal cases because we are afraid of causing serious toxic effects in the treatment of a disease which has an almost uniformly favorable prognosis when treated by methods known to be safe.

VISITOR: If the organism becomes streptomycin-resistant, is the infection any more dangerous?

DR. MCDERMOTT: That is a problem which has concerned us and about which there is no information. It certainly should be investigated. We must find out whether the continued administration of streptomycin after development of streptomycin-resistance produces a more fulminating type of infection.

DR. GOLD: How do you view the mechanism of the very rapid development of resistance to streptomycin in view of the more or less generally accepted idea that the development of resistance is due to the breeding out of resistant strains? Why does that happen so quickly in the case of streptomycin and relatively slowly in the case of penicillin? It is fundamentally the same type of process, breeding out the tolerant or resistant members of a strain.

DR. MCDERMOTT: I think that the development of bacterial resistance proceeds by several mechanisms; breeding out is only one; mutation is another. There is evidence

that adaptive enzymes can be developed by bacteria. The selective breeding of chance developing mutants is generally believed to be the most reasonable explanation for most instances of the recognized resistances. Most organisms against which penicillin is effective show remarkable uniformity in their sensitivity *in vitro* among the individual members of a species. There are some exceptions such as the staphylococcus. It seems to be otherwise for streptomycin. The Escherichia coli against which streptomycin is so effective, for example, shows rather wide differences in the susceptibility of members of a species. A fundamental difference in the point of attack on the vital functions of the bacterial cells in the case of the two drugs may be one factor in explaining the ease with which streptomycin produces bacterial resistance. This applies to the mechanism of breeding out resistant members as well as to any other mechanisms by which resistance within bacterial cells may be developed.

INTERN: I would like to ask if the kidney damage caused by streptomycin is permanent or reversible?

DR. MCDERMOTT: Some of it is certainly reversible. We had one patient, about thirty years old, who, in the course of a very serious tuberculous pneumonia, developed evidence of fairly marked renal damage during a sixty-day period of streptomycin therapy. The urea clearance fell to about 40 per cent of normal. During the second sixty-day period of treatment the renal damage subsided concurrently with the improvement in the tuberculous pneumonia. Another patient, who had only one kidney, suffered renal damage during the first course of treatment with streptomycin. A second course of treatment for ninety days, however, produced no further apparent damage, the blood urea nitrogen remaining somewhat above 30 mg. and the urea clearance below 20 per cent of normal.

DR. CATTELL: I would like to ask Dr. McDermott if he has tested the resistance of the organisms in the tuberculous patients before using streptomycin?

DR. MCDERMOTT: We have in every case and all of them were sensitive. This was also the case with the organisms which were tested by Dr. Youmans in Dr. Hinshaw's studies. I must emphasize that the conditions of the test are not such as to give one a wide sampling of the individual cells in a particular culture. No one has as yet carried out the necessary test of streaking out the culture and testing a number of different cells for sensitivity.

DR. GOLD: Do not all routine *in vitro* tests for sensitivity suffer from the same defect, namely, that they fail to separate out resistant from sensitive members in the sample which is being tested?

DR. MCDERMOTT: That is so, Dr. Gold when the test is performed in liquid media. It is not so when the organisms are plated out. That is what is being done in the case of the staphylococcus, for example.

INTERN: I would like to ask if streptomycin has an effect on the hematopoietic system? I remember one patient in whom the platelet count dropped from 350,000 to around 40,000 after streptomycin administration. When the streptomycin was discontinued, the platelet count returned to normal.

DR. MCDERMOTT: Was there any bleeding?

SAME INTERN: Yes, there was bleeding when the count was at the low point. The bleeding was the reason for the count. This patient had had typhoid fever and the gallbladder was removed because he was a typhoid carrier. He then developed a typhoid abscess in the operative wound for which the streptomycin was given.

DR. MCDERMOTT: Was he receiving a sulfonamide?

SAME INTERN: No.

DR. MCDERMOTT: Such a reaction might be expected after a sulfonamide but I have never encountered it after streptomycin. There is a report of a patient with acute brucellosis treated with streptomycin who developed thrombocytopenic purpura from which he recovered completely. We have seen leukopenia and in one case it was associated with granulocytopenia. We have seen these reactions in patients with acute miliary tuberculosis in whom the possibility

of bone marrow involvement was also present.

DR. MUSCHENHEIM: Dr. Bunn told me of a patient with miliary tuberculosis who developed granulocytopenia which improved after the discontinuation of streptomycin. This seemed to rule out bone marrow infection due to tuberculosis.

DR. GOLD: Dr. McDermott, will you say something about the dosage and the preparations?

DR. MCDERMOTT: By great good fortune, the original unit of streptomycin coincided with 1.0 microgram of the active substance. This makes it convenient, therefore, to express dosage in terms of weight of the drug.

DR. GOLD: Are doses expressed in terms of the pure crystalline substance?

DR. MCDERMOTT: Yes, in terms of the pure streptomycin base. The material which is marketed is in the form of the hydrochloride or the sulfate and it is not pure. The label on the vial indicates the amount of the pure base to which the contents of the vial is equivalent. Thus, in a vial labeled as equivalent in activity to 1 Gm. of streptomycin base, the actual weight of the material in the vial may be greater than 1 Gm. because of the impurities. Because of the differences in the amount of impurities in different preparations, two vials labeled 1 Gm. streptomycin may contain different amounts of material while both represent the activity of the same amounts of pure streptomycin.

The material is soluble in water. It can be administered dissolved in distilled water. It is usually given by intramuscular injection.

For most infections, 1 to 3 Gm. daily is adequate. In tuberculosis, Dr. Hinshaw's group first used 1 Gm. and then 1.5 Gm. We used 3 Gm. from the beginning. There is no evidence that our patients have done any better than Dr. Hinshaw's. There is no evidence that large initial doses prevent the development of bacterial resistance; at least bacterial resistance has not been prevented by even such large doses of streptomycin as cause toxic effects. For most urinary tract infections, I think 1 Gm. per day should be sufficient. In Hemophilus influenzal meningitis, the dose depends on the size of the child. I think 0.1 Gm. is the upper limit of safe dosage in an adult when the drug is administered by the intrathecal route. Larger doses than that are sometimes tolerated but are sometimes associated with toxicity. We would therefore advise using single doses of streptomycin no larger than 0.1 Gm. when given by the intrathecal route.

DR. GOLD: Do you prefer the interrupted intramuscular method of administration?

DR. MCDERMOTT: Usually I do. In a nonfulminating infection, I would say that therapy during eighteen of the twenty-four hours would be adequate. In a fulminating infection, such as Hemophilus influenzal meningitis, injections should be given at three-hour intervals around the clock.

DR. GOLD: Not by intravenous injection?

DR. MCDERMOTT: It is unnecessary.

DR. JANET TRAVELL: Does the material cause pain?

DR. MCDERMOTT: Yes, the commercially available material of the past two years was painful to a variable degree. Highly purified crystalline material, at least 95 per cent pure, such as we used in the tuberculosis study, is no more painful than the best penicillin preparations.

DR. GOLD: Is there any material on the market that is as pure as the standard against which the streptomycin of commerce is compared in the assay?

DR. MCDERMOTT: No, but I believe that the large manufacturers are soon going to have on the market material of about the same grade of purity as the highly purified material which we used.

DR. TRAVELL: Will that increase the cost?

DR. MCDERMOTT: It increases the cost to the manufacturers considerably because they lose about 50 per cent of the yield in the crystallization. I doubt that it will materially increase the cost to the public in a competitive market if there is enough demand for it.

DR. PEARLMUTTER: Has streptomycin been given a trial in virus pneumonia?

DR. MCDERMOTT: I do not know of any instances in which it has but I assume that it has. I would certainly be opposed to using it in atypical pneumonia. Although the drug is relatively non-toxic in comparison to some drugs, it is not innocuous and not to be used for self-limited, benign infections.

DR. GOLD: How does the problem of oral administration stand at the moment? Animal experiments show that it is absorbed by the oral route and that the fatal dose, by mouth, in mice, is just about three times that by subcutaneous injection. I am wondering whether the situation here is analogous to the case of penicillin in which, if we give something like five to ten times the parenteral dose, we might obtain perfectly satisfactory effects by the oral route. Have you any opinion about that?

DR. MCDERMOTT: We have not pursued the subject because of the scarcity of the material.

VISITOR: At Bellevue Hospital a series of typhoid carriers was examined. First, the drug was given intravenously. There was no conspicuous effect on the typhoid organism. There was a high incidence of renal toxicity among these patients. Some of them were given the drug orally. There was apparently less renal irritation. For a time the stool cultures were negative but subsequently reverted to positive. I am not certain of the range of dosage when it was given orally; I think it was of the order of twice the intravenous dose.

ANOTHER VISITOR: Is it possible to inject streptomycin intramuscularly in wax and oil to avoid multiple injections as is now often done with penicillin?

DR. MCDERMOTT: Unfortunately, that is not practicable because the amount of the drug which would be given in such a fashion would be too large, much greater than that in the case of penicillin.

INTERN: At a recent therapy conference on urinary tract infections we were left with the impression that the sulfa drugs are far more useful in these infections than streptomycin. I wonder if you share those sentiments?

DR. MCDERMOTT: In uncomplicated infections of Escherichia coli, which is the most common infection of the urinary tract seen by the internist and the obstetrician, I believe that sulfadiazine should be used first. While streptomycin is very effective against the Escherichia coli urinary infections, its greatest value in infections of the urinary tract does not apply to the Escherichia coli infections but to the infections by other organisms in the urinary tract and in those complicated by bacteremia or metastatic abscesses arising in association with obstructions of the urinary tract.

DR. GOLD: Dr. McDermott, as matters stand at the present time, would you be inclined to give streptomycin a trial in any infection which was found not to respond to penicillin or a sulfa drug, irrespective of whether the organism involved was a coccus or bacillus, gram-positive or gram-negative? To be sure, experience with streptomycin in some infections such as typhoid fever, bacillary dysentery and undulant fever has been disappointing and, in those few instances, one might be justified in withholding the drug but how about the large variety of other infections? Is the scope of streptomycin uses sufficiently defined to justify its omission in an infection in which penicillin and the sulfa drugs were considered and tried but proved ineffectual and in which it now seems that the patient is likely to die unless the infection is controlled?

DR. MCDERMOTT: Yes, I think that streptomycin should be tried since there is evidence that some one of these agents will affect most bacterial infections. The virus infections are exceptions. I do believe, however, that reasonable indications should be present before streptomycin is used because of its fairly high toxicity.

DR. GOLD: Might you possibly first make an *in vitro* test for the susceptibility of the organism?

DR. MCDERMOTT: Yes, that would help.

DR. GOLD: I am afraid our time is up.

SUMMARY

DR. MODELL: The conference this afternoon was on the subject of the uses of streptomycin. The experiences with the sulfa drugs and penicillin have been put to good use in speeding up the steps necessary for the proper clinical evaluation of this new antimicrobial agent and now, only about three years after the first clinical reports on streptomycin, a formidable volume of information has accumulated concerning its actions and uses. The material is now available in a highly purified form. Since, however, it still contains some impurities, varying in amounts in different preparations, a biologic assay is applied to the different lots. It is less confusing to express dosage in units of weight rather than in biologic units and, therefore, the labels on the vials describe the contents in terms of Gm. of pure streptomycin base. Streptomycin is freely soluble in water. It is suitable for all the common routes of administration. Not enough is known about its absorption by oral administration and it does not seem to be useful for systemic action by the oral route. It is most commonly given by intramuscular injection in divided doses. A dose of 2 to 3 Gm. daily appears to be adequate for the majority of infections in which it is useful. Larger doses are likely to cause too high an incidence of toxic effects.

Streptomycin is effective against most of the organisms which are inhibited by penicillin. In addition, however, it exerts a potent action against gram-negative organisms which are uninfluenced by penicillin. While bacteriologic experiments suggest a very wide field of usefulness for streptomycin, direct experience in the treatment of human diseases has greatly restricted the scope of its application. Experience thus far indicates that penicillin is preferable in those infections in which either of the drugs might be used because penicillin is non-toxic while streptomycin possesses toxic actions which are sometimes quite serious. There is also the fact that penicillin is administered in quantities measured in milligrams and streptomycin in quantities of grams and these large amounts of the drug are not practical for some of the special technics of administration such as suspension in wax and oil for delayed absorption. Thus far, streptomycin has been found especially useful in urinary infections caused by the Escherichia coli and some other gram-negative bacterial infections of the urinary tract such as the Bacillus lactis aerogenes, Bacillus proteus and Bacillus pyocyaneus. It is highly effective in Friedländer's pneumonia, Hemophilus influenzae meningitis and tularemia. It has also been found effective in pneumonias, abscesses, peritonitis and other infections caused by the gram-negative bacteria frequently found in the urinary tract. It appears to be without value in virus infections. One of the most stirring aspects of streptomycin action is the observation that it cures certain forms of animal tuberculosis and the now well established clinical experience showing that it may check some forms of human tuberculosis, especially those in the exudative stage. There was considerable discussion in the conference concerning the details of its rôle in the therapy of human tuberculosis.

Two other phases of streptomycin therapy received special consideration. There is some indication that different members of the same bacterial species show wide differences in susceptibility to streptomycin and it is now well established that for most infections, resistance to streptomycin is acquired quite rapidly, in a matter of days to weeks. This limits the application of the drug to brief courses of treatment and necessitates the use of fully effective doses from the outset. The next point is the matter of toxicity. Streptomycin is not an innocuous drug. In addition to the various allergic drug reactions such as skin rash and fever, it may produce serious renal damage, it may affect the blood-forming organs and it exerts an action on the central nervous system involving the vestibular apparatus and the eighth nerve causing vertigo, tinnitus and impaired hearing, some of the effects becoming permanent. These effects are apt to occur after prolonged use of the drug,

after three or four weeks. They are more frequent with the larger doses, doses larger than those usually necessary. One needs to keep them in mind, however, for the full scope of the applications of streptomycin has not yet been established and a good deal of exploration is still necessary to establish the full potentialities of streptomycin in human infections. In the present state of our knowledge, there is justification in giving streptomycin a trial in serious bacterial infections in which the other specific antimicrobial agents have failed. It is suggested that an *in vitro* test of the sensitivity of the organism may help to establish the indication for its trial in such cases.

Clinico-pathologic Conference

Rheumatic Heart Disease, Bacterial Endocarditis and Cardiac Failure*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, L. B., (B. H. No. 118183), a twenty-two year old white, married draftsman, entered the Barnes Hospital for the first time on September 22, 1944, complaining of weakness. The family history was non-contributory. The past history revealed that the patient, in addition to the usual childhood diseases, had had scarlet fever at the age of six years and, subsequently, his mother had been told that the patient's heart had been damaged. At the age of nine, he was said to have had "rheumatism" for several days but he could recall no specific symptoms. From that time on he had been a thin, nervous individual who lacked physical endurance but he had had no further significant illnesses. His habits were good.

Six months before entry, the patient was given digitalis by his family physician although he could give no history of any cardiac symptoms at that time. He took the medication for one month and then discontinued it because of nausea. About seven weeks before entry, he developed increasing fatiguability, so much so that he often fell asleep while working and at night slept twelve hours; his appetite also decreased. About five weeks before admission, the patient had a tooth extracted and a few days thereafter he noted the onset of fever which at one time was said to have been as high as 104°F. A non-productive cough, associated with generalized aching pains in the chest and left arm, began and the patient again consulted his family physician who made a tentative diagnosis of tuberculosis; a chest film was negative, however, and the diagnosis was changed to chronic bronchitis.

One month prior to entry, small, painful red spots appeared on the tips of the patient's fingers and toes and a week later he began to note palpitation and dyspnea on exertion. Two weeks later, his ankles swelled and he was admitted to a rural hospital where he was given a sulfonamide drug four times daily for four days. He became very nauseated and totally anorexic and was transferred to the Barnes Hospital.

At the time of entry, his temperature was 37°C., pulse 92, respirations 24 and blood pressure 94/50. The patient was a well developed but poorly nourished, young, white male who lay quietly in bed and appeared chronically ill. The skin was pallid. Petechiae were noted on the skin of the back, hands and feet and there were small, tender, red lesions on some of the finger tips. The joints appeared normal. The conjunctivae were clear. The pupils reacted well to light and accommodation and fundoscopic examination was negative. The teeth were carious and the gums exhibited signs of infection. Examination of the lungs revealed them to be clear to percussion and auscultation. On inspection, the heart appeared hyperactive; a heaving

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impulse occupied most of the precordium and a systolic thrill was easily palpable. On percussion, left border dullness enlargement extended 14 cm. in the fifth interspace and 13 cm. in the sixth interspace and right border enlargement was 3.5 cm. in the fourth interspace. The first sound was obscured by a very rough, harsh, blowing systolic murmur which could be heard all over the precordium as well as posteriorly. A mid-diastolic, low pitched, rumbling murmur was audible at the apex. The rhythm was regular. The spleen was palpable 4 cm. below the left costal margin and was slightly tender. The remainder of the abdominal examination was negative; there was no clubbing and the neurologic examination was within normal limits.

The laboratory findings were as follows: Blood count: red cells, 4,320,000; hemoglobin, 12.5 Gm.; white cells, 9,500; differential count; juvenile forms, 2 per cent; stab forms 27 per cent; segmented forms, 60 per cent; lymphocytes, 11 per cent. Urinalysis; albumin, trace; sediment, occasional hyaline cast and occasional red blood cell. Stool examination: negative. Blood Kahn test: positive. Blood chemistry: non-protein nitrogen, 18 mg. per cent; total protein, 6.1 Gm. per cent; albumin, 3.5 Gm. per cent; globulin, 2.6 Gm. per cent. Blood sulfadiazine level (on entry): 10.5 mg. per cent. Venous pressure: 125 mm. of saline. Circulation time (decholin): 16 seconds. Vital capacity: 2700 cu. cm. Roentgenogram of the chest: "The cardiac silhouette is enlarged to the left and somewhat to the right. It has a globular appearance with prominence in the region of the pulmonary artery. The aorta is inconspicuous. There is tenting and irregularity of both leaves of the diaphragm, presumably as a result of adhesions from old pleurisy." Electrocardiogram: slurring and notching in lead I; T waves low upright.

Five consecutive blood cultures taken shortly after the patient entered the hospital were positive for alpha-hemolytic streptococci. A swinging temperature curve persisted and showers of new emboli were observed. As soon as the blood culture results were known, penicillin was instituted in a dosage of 40,000 units every two hours intramuscularly. There was a prompt response to therapy as indicated by a fall in temperature and a great decrease in the number of emboli. The urine became entirely negative and subsequent blood cultures were all sterile. The blood Kahn test was repeated and on titration revealed 40 Kahn units. The patient denied any lesions suggestive of primary or secondary syphilis and no further antisyphilitic therapy was instituted during the hospital stay.

The patient continued to receive penicillin for nineteen days after which it was discontinued; he received a total of 5,850,000 units. He left the hospital on November 5th, 1944, to be followed in the Clinic.

Following discharge, the patient did progressively well. He had no further fever nor petechiae and three months after discharge was well enough to resume his work as a draftsman. Five months before his second admission, he had a number of teeth extracted at weekly intervals, each time with sulfadiazine prophylaxis. He was followed in the Clinic where his general condition continued to be good except that he failed to gain weight despite an excellent appetite. He was advised to re-enter the hospital in order to ascertain the cause for his failure to gain weight.

He was admitted on July 9, 1945, at which time the temperature was 37.2°c., pulse 100, respirations 24 and blood pressure 128/65. He appeared quite well. No petechiae were observed. The only changes in physical examination from those recorded on the previous admission were as follows: a definite early high-pitched diastolic blow was heard over the aortic area and along the left sternal border. The pulses were fuller than before and the pulse pressure had increased. The liver edge was felt 1 to 2 cm. below the costal margin. It was thought by one observer that the fingers were slightly clubbed.

Laboratory studies revealed the blood count, urinalysis and stool examination to

be entirely within normal limits. The blood Kahn test was negative. The vital capacity was 4400 cu. cm. and the corrected sedimentation rate 0.1 mm. per minute. The electrocardiogram showed only a full P-R interval. Because of the previously positive serologic test for syphilis, a lumbar puncture was performed and the findings were entirely negative. During his hospital stay the patient's course was entirely uneventful and he was discharged on July 14, 1945, to be followed in the Clinic.

He did quite well for a number of months, working as a radio repair man. One month before his third hospital admission, he developed an upper respiratory infection which was followed by a non-productive cough; at no time did he have fever. He recovered from the respiratory infection but subsequently had increasing dyspnea on exertion which soon became so severe as to incapacitate him. He also had episodes of paroxysmal nocturnal dyspnea and complained of frequent palpitation. Progressive edema of the ankles likewise appeared and the patient gained approximately 6 pounds. One week before entry, he noted pain in the upper abdomen and a feeling of fullness after meals. He had no other digestive symptoms nor had he had pain in the chest, night sweats or fever. He was readmitted to the hospital on March 5, 1946.

At the time of entry, his temperature was 37°C., respirations 24, pulse 90 and blood pressure 110/70. He appeared rather ill and in moderate respiratory distress. Orthopnea was particularly notable. There was a frequent, dry, hacking cough. The neck veins were markedly distended. There was some diminution of breath sounds over the right posterior chest but definite signs of fluid were not made out. A heaving precordial pulsation extended to the left midaxillary line and the heart rate was 128 at the apex. The rhythm was irregular. The same harsh, systolic murmur previously noted was present and P_2 was accentuated. In the aortic area, the sounds were muffled and a diastolic murmur could not be made out. The liver extended 5 cm. below the costal margin and was smooth and tender. The spleen was questionably palpable. There was 1+ ankle edema.

The laboratory findings were as follows: the red count, hemoglobin, white count and differential count were normal. Urinalysis: specific gravity, 1.022; albumin, 1+; sediment, negative. Stool examination: negative. Blood Kahn test: negative. Venous pressure: 240 mm. of saline. Circulation time (decholin): 44 seconds. Blood chemistry: non-protein nitrogen, 25 mg. per cent; total protein, 4.6 Gm. per cent; albumin, 3.1 Gm. per cent; globulin, 1.5 Gm. per cent. Blood cultures: no growth. Electrocardiogram: low voltage in lead I; auricular fibrillation, right axis deviation.

The patient was digitalized with digitoxin; his venous pressure soon fell to 140 mm. of saline and the circulation time to 30 seconds. Dyspnea, orthopnea, ankle edema and cough all disappeared and on a salt-free diet the patient became quite comfortable. He left the hospital on March 17, 1946, with instructions to maintain a salt-free diet and to take 0.2 mg. of digitoxin daily. Once during his hospital stay, one observer again described an early diastolic murmur at the aortic area and along the left sternal border. At no time were any of the peripheral manifestations of bacterial endocarditis noted.

Following discharge, the patient was essentially symptom-free except for mild dyspnea on exertion. One month before his fourth admission, he had the onset of two-pillow orthopnea and his ankles again began to swell. He had no fever, chest pain or any digestive disturbances. He re-entered the Barnes Hospital on July 1, 1946.

The findings on physical examination included a temperature of 37.2°C., pulse 84, respirations 18 and blood pressure 124/80. Physical examination was essentially unchanged from that recorded on the third admission except the neck vein distention was not so marked. Auricular fibrillation was again described and the liver, which was palpable 4 cm. below the right costal margin, was tender. The spleen could not be felt. No clubbing or edema was described.

The routine blood studies were all normal. The urine was negative except for a small amount of albumin. Blood cultures were all sterile. The venous pressure was 220 mm. of saline and the circulation time with decholin was 55 seconds. Films of the chest revealed no new findings. An electrocardiogram showed auricular fibrillation, right axis deviation, ventricular premature contractions and questionable digitalis effect.

The patient was seen in consultation by the dental surgeon and extraction of two badly diseased teeth was advised. Penicillin was given prophylactically and the teeth removed under local anesthesia. Subsequent to extraction, repeated blood cultures continued to be sterile and at the time of discharge on July 12, 1946, the patient was essentially symptom-free. He was again instructed to maintain a salt-free diet and to continue digitoxin. During his stay he had had no fever.

In the eight weeks following discharge, the patient had a gradual but progressive increase in dyspnea, ankle edema and nonproductive cough and on September 6, 1946, he was re-admitted for evaluation of his cardiac status.

The findings on physical examination were not significantly changed from those noted previously. The laboratory findings of interest were a white count was 19,650; the differential count showed 2 per cent basophiles, 4 per cent eosinophiles, 12 per cent stab forms, 49 per cent segmented forms, 23 per cent lymphocytes and 10 per cent monocytes. Urinalysis revealed rare granular casts in the sediment. The venous pressure was 210 mm. of saline and the circulation time with decholin was 50 seconds. The total proteins were 4.7 Gm. per cent with 3.3 Gm. per cent of albumin and 1.1 Gm. per cent of globulin.

The patient remained in the hospital eight days; rest in bed combined with a salt-free diet and digitoxin were sufficient to restore cardiac compensation. He left the hospital on September 14, 1946, to continue the same therapeutic regimen.

He did fairly well and was able to return to his work as a radio repair man. He was followed in the Clinic where he was given mercupurin intravenously at frequent intervals; prior to each administration of mercupurin, he took ammonium chloride. Digitoxin therapy was likewise continued but, despite these measures, the patient's ankle edema recurred and he developed increasing dyspnea both on exertion and at rest. Likewise, paroxysmal nocturnal dyspnea reappeared and his cough became worse. He remained at home in bed for several weeks during which period flatulence and belching likewise occurred; he complained of severe nausea but did not vomit. He entered the Barnes Hospital for the last time on December 12, 1946.

At that time, he appeared poorly nourished, depressed and extremely ill. Orthopnea was marked but there was no cyanosis. The significant physical findings included marked venous distention and a massive right hydrothorax. The heart was greatly enlarged and the precordial impulse was so severe as to shake the patient's entire chest with each beat. Rapid auricular fibrillation was present with a marked pulse deficit and a harsh, grade IV, blowing, systolic murmur could be heard all over the thorax. A mid-diastolic rumble was likewise audible at the apex. At the base, the grade IV systolic murmur could be heard but no aortic diastolic murmur could be made out. The liver extended 8 cm. below the costal margin. The spleen and kidneys were not palpable. There was 3+ pitting edema of the ankles extending up to the knees.

Laboratory findings were as follows: the complete blood count, urinalysis and stool examination were all within normal limits. Blood Kahn test: negative. Venous pressure: 300 mm. of saline; circulation time (decholin): 75 seconds. Blood chemistry: non-protein nitrogen: 22 mg. per cent; CO_2 combining power, 51.8 vol. per cent; chlorides, 92 mEq./liter. Blood culture: negative. Roentgenogram of the chest: "There is extensive enlargement of the cardiac shadow. The aortic knob cannot be seen. There is a prominence of the cardiac

shadow in the region of the pulmonary conus and left auricle. Compared with previous films there has been some increase in heart size. The lungs show evidence of congestion but otherwise are normal except for the diaphragmatic adhesions previously present." Electrocardiogram: auricular fibrillation, digitalis effect and right axis deviation.

The patient was placed on a regimen which included complete bed rest, a salt-free diet, digitoxin 0.1 mg. twice daily, ammonium chloride 1.0 Gm. three times daily and mercuhydrin 2.0 cc. every other day. Despite these measures, he failed to improve; indeed, his dyspnea and orthopnea increased and he was placed in an oxygen tent. Because of persistent nausea and vomiting, he was unable to take adequate food or fluids by mouth and had to be fed parenterally. The non-protein nitrogen gradually rose and before the patient's death reached a level of 111 mg. per cent. During his entire hospital course the patient remained afebrile. The sedimentation rate was within normal limits. His white count likewise was never elevated. In an attempt to achieve some degree of cardiac compensation, digitoxin was given intravenously in doses totalling 0.3 mg. daily but it was not effective; the marked pulse deficit persisted and the patient continued to do poorly. The possibility of acute rheumatic fever as an explanation of the patient's poor response to digitalis was raised and salicylate therapy was instituted but it likewise was without favorable results. The patient became obtunded and subsisted on subcutaneous 5 per cent glucose in water. The apical cardiac rate and pulse deficit increased further; breathing became slow, irregular and gasping and the patient lapsed into a coma. Death occurred on December 21, 1946.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient had a long history which illustrates many of the essential features of rheumatic endocarditis. The onset of the process apparently occurred when he was six years old and when he was twenty-two he developed subacute bacterial endocarditis due to the alpha-hemolytic streptococcus. The latter complication was apparently cured by penicillin but subsequently recurrent cardiac failure appeared and finally led to death. Let us consider first of all the onset of the rheumatic disease. According to the history, this man had scarlet fever when he was six years old and very shortly thereafter his mother was told that his heart had been effected. This sequence of events raises the question of the relation of scarlet fever to rheumatic fever. Dr. Harford, would you open the discussion of this point?

DR. CARL G. HARFORD: Scarlet fever is considered to be one of the streptococcal infections which may precipitate an attack of acute rheumatic fever.

DR. ALEXANDER: Is that opinion well accepted or is there some debate about it?

DR. HARFORD: There are probably some differences in the views of various interested and informed persons but certainly the majority favor this concept which was set forth by Dr. Homer Swift, among others.

DR. ALEXANDER: Dr. Massie, would you care to comment?

DR. EDWARD MASSIE: I think the sequence described in this case is not an unusual one. Of course, scarlet fever *per se* need not occur, since a patient may have a streptococcal infection of the throat without a rash and develop rheumatic fever in much the same way. In other words, the manifestations of the original streptococcal infection may differ in various individuals whereas its relation to rheumatic fever is the same in all of them.

DR. ALEXANDER: We may, therefore, assume that the historic events outlined are not unusual and that this patient developed rheumatic fever as a consequence of scarlet fever when he was six. He did well from that time until he was twenty-two years old. He apparently received digitalis six months before his first admission here but we are unable to state why since he denied any cardiac symptoms at the time.

Seven weeks before his first entry, however, he noted the onset of fatigue and anorexia. Two weeks later, a tooth was extracted and one week after that and three weeks after the onset of fatigue, he had emboli and many of the signs and symptoms of bacterial endocarditis. Do the signs and symptoms of that disease usually develop over such a short period of time, Dr. Harford?

DR. HARFORD: I think it is a little difficult to be sure how long the patient actually had the disease.

DR. ALEXANDER: According to the history, three weeks elapsed from the onset of fatigue, which was his first complaint, to the time he noted emboli. What is your feeling on this subject, Dr. Massie?

DR. MASSIE: I saw this man in consultation at another hospital and was quite impressed by the rapidity of the development of the disease; indeed, I believed that it was one of the most rapidly developing cases I had ever seen. When I saw him, the diagnosis of bacterial endocarditis seemed quite clearcut and because at that time we were one of the clinics studying the effect of penicillin treatment on bacterial endocarditis, the patient was transferred to the Barnes Hospital. I might say that when I questioned the patient I had the impression that his symptoms prior to dental extraction were not particularly severe and I believed that the bacterial endocarditis was secondary to the extraction. In that case, the manifestations of the disease developed within a week.

DR. ALEXANDER: Are you impressed with the fact that he had no anemia when he was admitted, Dr. Moore?

DR. CARL V. MOORE: Anemia is certainly a characteristic finding in subacute bacterial endocarditis but there are cases such as this one in which anemia is not present.

DR. ALEXANDER: It was my feeling that anemia had not yet developed because of the very short duration of the entire process. After the diagnosis was confirmed by a number of positive blood cultures, the patient received 40,000 units of penicillin every two hours intramuscularly for nineteen days, a total dosage of almost 6,000,000 units. Dr. Harford, what is the suggested period of treatment for this disease?

DR. HARFORD: In general, we believe that treatment should be continued for a longer period of time than was used in this case. We have seen relapses occur after two or three weeks of therapy and now believe that a period of six weeks is advisable. This man was treated at a time when penicillin was scarce and, therefore, the duration of treatment was shorter than would be used today.

DR. ALEXANDER: Would you comment on the dosage?

DR. HARFORD: The dose, of course, must be adjusted to that level which controls the disease. We usually begin with a dose of 50,000 units given every two hours intramuscularly. If sensitivity tests are done, a dose is usually advised which achieves blood levels four or five times the *in vitro* sensitivity of the organism. The clinician must base his judgment as to the efficacy of a given dosage on the temperature response, the results of repeated blood cultures and the patient's general clinical condition. If the original dose fails to control the process, the dosage should be doubled or even quadrupled.

DR. ALEXANDER: How frequently is drug-fastness observed?

DR. HARFORD: We observed two cases out of twenty-one in which the streptococcus recovered was definitely resistant to penicillin.

DR. C. V. MOORE: It is interesting, in considering the dosage that this patient received, to note that Dr. Loewe in some instances had given as high as 10,000,000 units per day in the treatment of penicillin-resistant organisms but even doses of that magnitude did not control all the cases in which the causative streptococcus was highly penicillin-resistant.

DR. MASSIE: Dr. Alexander, do you think that the very short duration of the patient's illness prior to treatment favors the good

results obtained with the relatively small dose over a short period of time?

DR. ALEXANDER: That thought occurred to me and I am going to ask Dr. Robert Moore to comment on that point when he shows us the microscopic sections. As you know, Dr. Moore has studied the healing process of this disease very carefully in patients treated with penicillin.*

This man's heart was extremely large. He had a loud, systolic murmur which could be heard all over the precordium and a low pitched diastolic rumble which was heard at the apex. From these signs, Dr. Massie, would you be able to predict the sites of the valvular lesions in the heart?

DR. MASSIE: Certainly the signs point to both mitral stenosis and mitral insufficiency. In addition, on several occasions an early basal diastolic murmur was heard and therefore one would consider the possibility that the aortic valve may have been insufficient.

DR. ALEXANDER: In view of the huge heart size, would you expect to find evidence of pericarditis?

DR. MASSIE: There may well be areas where the pericardial space is obliterated by fibrous adhesions but I doubt that physiologic constriction of the heart occurred. True constrictive pericarditis is rare in rheumatic heart disease.

DR. ALEXANDER: I was thinking more of pericardiomediastinal adhesions.

DR. MASSIE: I am sure that they will be found.

DR. ALEXANDER: Subsequent to his recovery from subacute bacterial endocarditis, the patient developed heart failure. Dr. Smith, I wonder if you would comment on the possible factors which led to his death?

DR. JOHN R. SMITH: When I saw this patient on his last admission, I was impressed with the possibility that he might have had acute rheumatic carditis in addition, of course, to severe cardiac failure.

DR. ALEXANDER: In other words, you would postulate a recrudescence of acute rheumatic fever. Does the fact that he had no fever during the entire terminal illness mitigate against the diagnosis of acute carditis?

DR. SMITH: No, not necessarily; temperature elevation need not be present in acute rheumatic carditis.

DR. ALEXANDER: Very large doses of salicylate were given without effect. Yet it is still conceivable that the patient had acute rheumatic carditis; if so, would you expect the pathologist to demonstrate histologic evidence of the process?

DR. SMITH: Yes, I would.

DR. ALEXANDER: Are there other comments?

DR. HENRY A. SCHROEDER: On his third admission, the patient was found to have developed auricular fibrillation; it is conceivable that the onset of the arrhythmia precipitated the mild degree of cardiac failure noted at that time and which was controlled rapidly by the use of one of the digitalis glucosides.

DR. ALEXANDER: Do you believe that the occurrence of auricular fibrillation here constituted a manifestation of chronic rheumatic heart disease?

DR. SCHROEDER: Yes, I do, particularly in view of the excellent response to digitalis.

DR. ALEXANDER: Dr. Massie, do you have any further comment?

DR. MASSIE: I think the possibility that this patient had recurrent episodes of acute rheumatic carditis is suggested by the change in cardiac murmurs. Progressive failure *per se* should not have been accompanied by the appearance of an aortic diastolic murmur. One other possibility is that the patient continued to have bacterial endocarditis, in the abacterial phase described by Libman, although I believe such an explanation is highly unlikely.

DR. ALEXANDER: Are there any other factors which may have contributed to the patient's downhill course?

DR. C. V. MOORE: Concomitantly with the healing of vegetations, the degree of valvular deformity may actually be ac-

* MOORE, R. A., The cellular mechanism of recovery after treatment with penicillin. I. Subacute bacterial endocarditis. *J. Lab. & Clin. Med.*, 31: 1279, 1946.

centuated and may lead to progressive, intractable cardiac insufficiency.

DR. ALEXANDER: I believe a similar chain of events was reported by Libman in several of his patients who recovered from the disease.

DR. HARFORD: We have seen a number of our other patients, successfully treated for subacute bacterial endocarditis, subsequently develop rapidly increasing cardiac failure which ultimately led to death. Such a sequence constitutes a tragic sequel to the successful treatment of this disease which, until the introduction of penicillin, carried a mortality rate which approached 100 per cent.

DR. ALEXANDER: Is it possible that the patient did not receive enough digitalis? It is true that he probably would have died eventually of cardiac failure in any case but it was obviously desirable to achieve complete digitalization.

DR. ROBERT J. GLASER: As noted in the protocol, 0.3 mg. of digitoxin were given daily by the intravenous route in an attempt to slow the cardiac rate and decrease the pulse deficit. Because we had very little else to offer this man, we believed we were justified in giving large amounts and we believed adequate dosage was given; indeed, it seems probable that he actually received an excessive quantity.

DR. PALMER H. FUTCHER: The patient's non-protein nitrogen rose to a rather high level during his terminal illness. The rise, of course, may well have been a manifestation of hypochloremia and heart failure but, on the other hand, the patient had had scarlet fever and bacterial endocarditis, both of which may give rise to renal damage. I would therefore raise a question as to the possibility of glomerulonephritis.

DR. ALEXANDER: In summary, it seems clear that this patient, who had rheumatic fever at the age of six, developed subsequent rheumatic heart disease. At the age of twenty-two, he contracted subacute bacterial endocarditis which was apparently cured by a course of penicillin therapy. Subsequent to his recovery, recurrent cardiac failure occurred and progressed, eventually failing to be controlled by all indicated measures and terminating in the patient's death. As possible explanations of the rapid downhill course following recovery from subacute bacterial endocarditis, several suggestions have been made; included, were acute rheumatic carditis and valvular damage secondary to the healing of bacterial endocarditis. Further valvular deformity from multiple attacks of rheumatic fever was also mentioned. As possible causes of azotemia, chronic glomerulonephritis or focal embolic nephritis were suggested.

Clinical Diagnoses: Rheumatic heart disease with mitral stenosis, mitral insufficiency and ? aortic insufficiency; cardiac insufficiency; subacute bacterial endocarditis, healed; ? acute rheumatic heart carditis; ? chronic glomerulonephritis or focal embolic glomerulonephritis.

PATHOLOGIC DISCUSSION

DR. OSCAR N. RAMBO: At autopsy, the body was that of a markedly emaciated man. There was marked edema of both lower extremities but no significant difference in the circumferences of the legs or thighs. Edema was also noted in the dependent portions of the upper extremities. On examination of the thorax, the most striking pathologic findings were in the heart. *In situ*, the apex was at the seventh rib in the mid-axillary line. The left transverse diameter measured 13 cm. and the right transverse diameter 7 cm. with a transthoracic diameter of 26 cm. The heart was globular in shape; there was marked dilatation of all chambers, particularly of the right atrium, right ventricle and pulmonary conus. There were no pericardial adhesions. The pericardial sac contained 200 cc. of dark yellow, cloudy fluid and in the epicardium of the right ventricle there was an irregular focal area of smooth fibrous thickening.

Internal examination of the heart showed dilatation and hypertrophy of the right atrium; the wall was 3 mm. thick. The tricuspid ring was dilated and the leaflets

were slightly thickened but not deformed. The wall of the right ventricle was 8 mm. thick. The left atrium was markedly dilated and its wall had an average thickness of 4 mm. In the endocardium of this chamber, there was a roughened, irregular area of yellow brown discoloration which lay inferior to the inferior pulmonary vein and superior to the posterior mitral leaflet. The mitral ring was slightly thickened, the leaflets showing diffuse fibrous thickening but no discrete nodules nor evidence of vegetations. The most significant change in the mitral valve was produced by thickening, shortening and fusion of the chordae tendiniae. Diffuse areas of endocardial thickening of a smooth, white fibrous nature were found posterior to the mitral valve and inferior to the aortic valve. The left ventricle was markedly dilated; its wall measured 14 mm. in thickness. The cusps of the aortic valve showed only slight, smooth fibrous thickening, most marked at their bases, and there were adhesions between the cusps at the commisures. This process involved only 1 to 2 mm. of the free edges and produced only slight deformity. The coronary ostia and vessels showed no gross abnormalities.

The combined weight of the lungs was 1,220 Gm. Both were firm, dark and congested with moist, dark red, cut surfaces. In the periphery of the lower lobe of the left lung, there was a firm, dark red pyramidal lesion measuring 6 by 5 by 4 cm., the cut surface of which showed partial obliteration of the alveolar pattern. In the lingula of the upper lobe of the left lung and in the upper and lower lobes of the right lung, there were lobular foci of consolidation, greenish in color, measuring 2 to 10 cm. in diameter. No pleural adhesions were present.

In the abdominal cavity, the liver was remarkable in that it weighed only 1,050 Gm. It was dark brown with dark red foci in the centers of the lobules and was slightly firm in consistency. The spleen was enlarged, firm and dark red; it weighed 320 Gm. Near the hilus, a small subcapsular triangular lesion measuring 6 by 5 by 4 mm. was found. It was yellow in color and fibrous in consistency. The kidneys were moderately enlarged, dark brown and firm with a few depressed scars, 2 to 5 mm. in their greatest dimension, on the cortical surfaces. The bladder was distended; its apex lay 7 cm. above the symphysis and it contained 800 cc. of dark yellow urine.

Dr. Robert A. Moore: This case presents interesting problems, both practical and theoretical, concerning whether or not the patient had subacute bacterial endocarditis and how the process was brought under control by penicillin two years before he died. In order to understand what has gone before, and before showing the microscopic sections, I would like to outline what appears to me to be the process of healing in bacterial endocarditis treated with penicillin and then to interpret the sequence in terms of this particular case. In a typical example of subacute bacterial endocarditis, there is a vegetation on the valve, the vegetation consisting anatomically of three parts. First, a central part which is necrotic, insofar as can be determined from looking at a microscopic section, next a layer of bacterial colonies and finally a thick layer of fibrin over the surface of the bacterial colonies, the layer of fibrin being approximately 500 to 750 micra in thickness. Similar vegetations form in the left auricular wall in the region that Dr. Rambo pointed out as being thickened in this case. Such vegetations characteristically are extremely small, very superficial and consist largely of bacterial colonies and a layer of fibrin; the vegetations which form on the left auricular wall do not have the large central necrotic core. There is instead a very small amount of necrotic material and the vegetations at this site characteristically never reach a large size. The healing process, insofar as can be determined, is as follows: the fibrous tissue grows up from the side and obliterates the layer of bacterial colonies and the layer of fibrin, forming a mass of fibrous tissue over the central necrotic mass. In several cases treated with penicillin which I have seen at

autopsy and in others reported from other laboratories, the central mass has undergone calcification. That is what Dr. Carl Moore had in mind when he pointed out that in the healing process of bacterial endocarditis, the valves may be further damaged to the point where the degree of valvular incompetence is actually increased; indeed, that is what happened clinically in most of the patients that have been reported so far in the pathologic literature.

When sections of the mitral valve of the patient under discussion were examined, there was only slight thickening and the thickening was uniform. The increase in size was caused partly by the thickening of the spongiosa on the auricular side of the valve and in part by the thickening of the fibrosa in the center of the valve. There was no significant change in the ventricularis on the ventricular side of the valve. The thickened valve did not show any swirling effects which are so frequently seen in the healing of both subacute bacterial endocarditis and rheumatic fever. It was the sort of valve that one would have expected to see in an individual who had had rheumatic fever as a child and had lived for ten or twenty years but not for thirty or forty years. Usually in a patient who dies at the age of thirty-five or forty and who had rheumatic fever in his youth, there is more thickening and many other manifestations, such as swirling in the connective tissue within the valve, rather than a uniform thickening which is characteristic of the earlier stages of valvular damage in rheumatic heart disease. I have no doubt, considering the history and the anatomic changes seen here, that this patient had rheumatic fever. I have serious doubt, however, that he had subacute bacterial endocarditis involving either the mitral or aortic valves although it is possible that he did. I have seen one example of subacute bacterial endocarditis in which the healing process did not leave the characteristic swirling or other deformity of the valve. In that case, I had always considered that the explanation of the absence of other changes lay in the fact that the patient's endocarditis was due to a pneumococcus, an organism extremely sensitive to penicillin. Perhaps the organism in this case was likewise extremely sensitive so that the process was brought under rapid control and left very little evidence of valvular scarring. On the other hand, as I pointed out to you purposely, the vegetation from the left auricular wall is characteristically small and heals without a great deal of scarring. I therefore would postulate, on the basis of the history and findings, that this patient's subacute bacterial endocarditis was confined to the left auricular wall; it was brought under control rapidly and thus a large vegetation on the mitral or aortic valve never developed.

There are several other features which are highly characteristic of subacute bacterial endocarditis: (1) the presence of multiple small abscesses in the myocardium which are due actually to small infected infarcts; (2) larger infarcts in the spleen and kidneys and finally (3) as has been pointed out in the clinical discussion, focal embolic glomerulonephritis which is never seen except in connection with subacute bacterial endocarditis.

Let us now consider the evidence in favor of the diagnosis of subacute bacterial endocarditis in the present case. The first section (Fig. 1) is of the myocardium, showing a miliary infarct in which the muscle has been destroyed. There is a loose connective tissue remaining which is moderately well vascularized and some of the remaining myocardial fibers show advanced fatty degeneration. I doubt if this lesion goes back two years. It is more likely of several months' duration. We were unable to find any lesions in the myocardium which could be identified as so-called Brach-Wächter bodies. In Figure 2, a section of kidney is seen; a few glomeruli have been destroyed and replaced by adhesions. I think the evidence favors the fact that this patient probably had focal emboli glomerulonephritis sometime before his death. Further, Dr. Rambo described an infarct in the spleen, a section showing dense fibrous tissue of the type which one would expect to see in an infarct

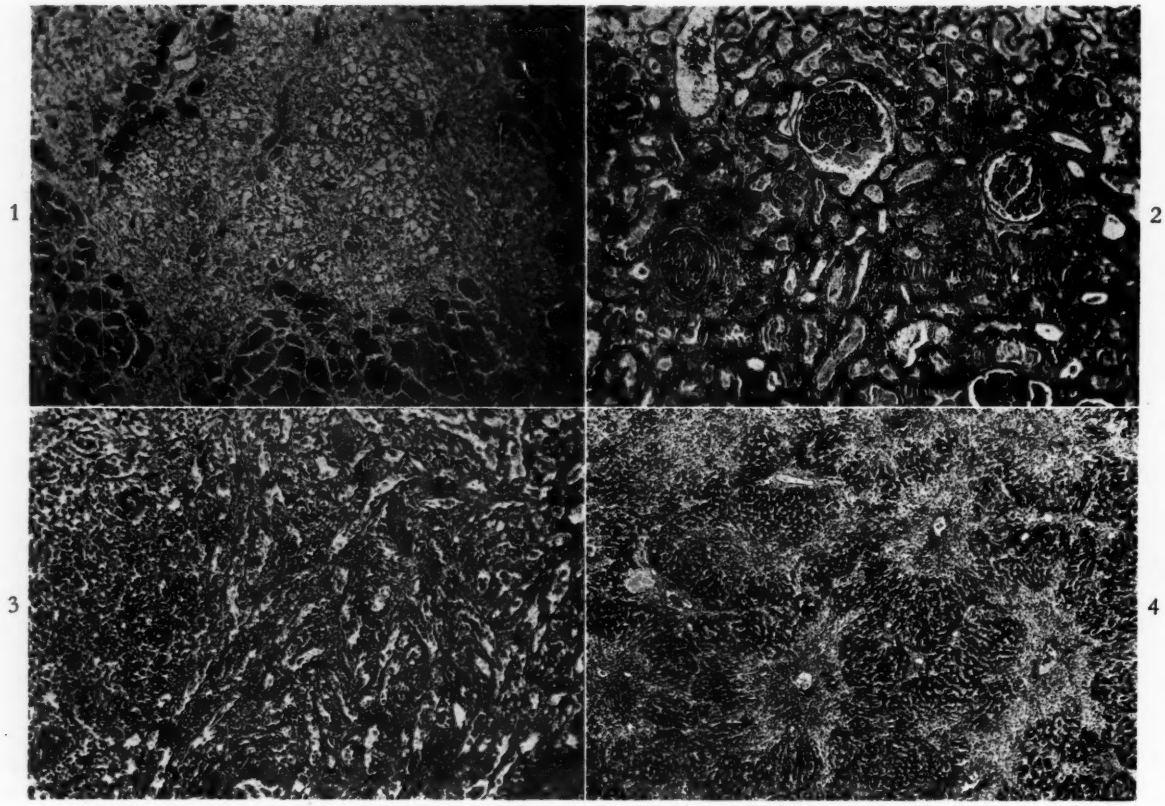

FIG. 1. Section of the myocardium showing a miliary infarct.
FIG. 2. Section of the kidney. Note that one glomerulus in this section has been destroyed.
FIG. 3. Section of the spleen showing the changes of advanced chronic passive congestion.
FIG. 4. Section of the liver again showing the changes of chronic passive congestion.

two years old. Thus, from these sections we can gather some evidence to support a diagnosis of subacute bacterial endocarditis.

The next two slides will illustrate the degree of chronic passive congestion. In Figure 3, a section of the spleen shows a characteristic glandular pattern with numerous large, dilated sinusoids lined by prominent cells, the so-called chronic spleen of advanced chronic passive congestion. In Figure 4, a section of the liver shows an advanced degree of chronic passive congestion. The regions have almost become confluent with the portal spaces isolated. The architectural pattern of the liver is reversed. This patient lost approximately one-half of his liver as a result of elevated venous pressure. In the sinusoids of the central regions there was also some proliferation of connective tissue. The lungs (Fig. 5) showed chronic passive congestion and other findings as well. Pneumonia, thickening of the alveolar walls, proliferation of connective tissue and a fair amount of hemosiderin from chronic congestion can be seen. There is some suggestion of rheumatic pneumonia although this diagnosis cannot definitely be made. In Figure 6, another illustration of the change of the lung is seen.

A different section (Fig. 7) of the myocardium shows vacuolization of the fibers in the hematoxin-eosin preparation and a fat stain (Fig. 8) demonstrates that this patient had a considerable degree of fatty metamorphosis of the myocardial fibers.

From these findings, it is clear that this patient had rheumatic heart disease and subacute bacterial endocarditis which probably involved the left auricular wall but not the aortic or mitral valves. The bacterial infection had been brought completely

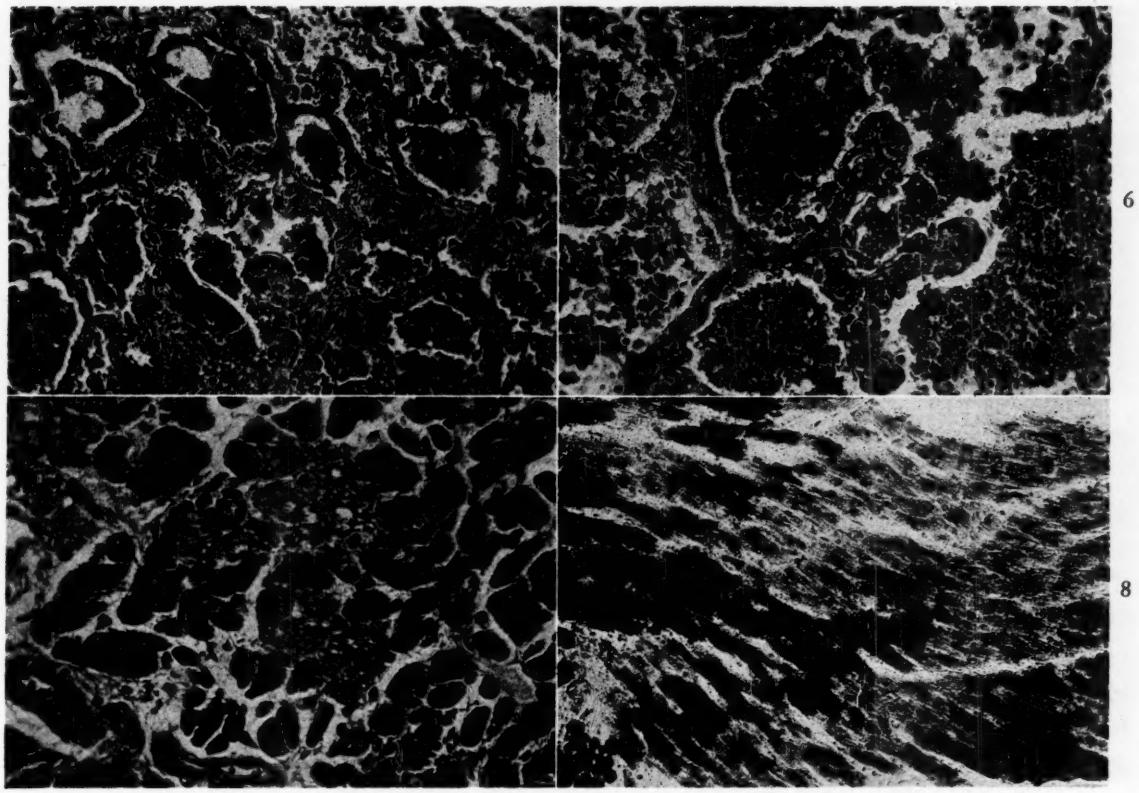

FIG. 5. Section of the lungs. The findings indicate both pneumonia and chronic passive congestion.
FIG. 6. Another section of the lung showing similar changes.
FIG. 7. Section of the myocardium showing vacuolization of the fibers. (H and E stain.)
FIG. 8. Section of myocardium stained for fat.

under control with a minimal amount of scarring. Then over a period of time, the heart failed and finally could not respond to treatment. No manifestations of acute rheumatic fever were noted. From an anatomic standpoint neither the mitral nor the aortic valves were damaged enough to explain the degree of hypertrophy and dilatation of the heart and it seems likely that at some earlier time, perhaps during the episode of subacute bacterial endocarditis, the patient suffered severe damage to the myocardium which caused the extensive dilatation and resulting hypertrophy. The patient finally succumbed, not of chronic valvular disease, but because of myocardial disease *per se*.

Anatomic Diagnoses: Chronic endocarditis of the mitral valve, moderate, and aortic valve, slight; (clinical history of rheumatic fever, sixteen years, and treatment of subacute bacterial endocarditis with penicillin following tooth extraction two years ago); hypertrophy and dilatation of the heart (675 Gm.); hydropericardium (200 cc.); chronic passive congestion of the lungs, liver, kidneys and spleen; recent infarcts of the upper and lower lobes of the left lung; bronchial pneumonia of the upper lobe of the left lung and upper and lower lobes of the right lung.

Case Report

Infectious Mononucleosis with Severe Central Nervous System Involvement

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CASES of infectious mononucleosis exhibiting signs of central nervous system involvement have from time to time been reported in the literature. Bernstein in his comprehensive review of the disease says that central nervous system involvement is occasionally encountered and that when it is, "the commonest initial symptoms in this form of the disease are headache, signs of meningeal irritation and blurring of vision. In certain instances there have been convulsions, stupor and coma."

In the majority of these patients signs of meningeal irritation have outweighed other central nervous system findings. Many have reported headache, positive Brudzinski and Kernig signs and an increase in the total lymphocyte count in the spinal fluid. In 1931, Epstein and Dameshek reported a case of a nineteen year old Russian-Jewish male who developed headache, blurring of vision and stupor. Lymphadenopathy and splenomegaly were present and lymphocytosis with atypical cells was reported. Subsequently, the patient developed a positive Brudzinski sign. There was a moderate increase of cells in the spinal fluid.

In 1941, Landes, Reich and Perlow reviewed the subject of central nervous system involvement in infectious mononucleosis and concluded that neurologic signs may be multiple: headache, photophobia, nystagmus, poor articulation, nausea and vomiting and positive Kernig and Brudzinski signs. Spinal fluid findings may also vary, the pressure may or may not be elevated. Pleocytosis may vary from 25 to 300 cells, the majority being lymphocytes. The spinal fluid protein may be increased as well as the globulin fraction. Their patient was admitted with headache, dizziness, vomiting and a staggering gait. The blood smears were typical of infectious mononucleosis but the lymphadenopathy and splenomegaly did not appear for three weeks after onset of the disease. Eleven days after onset the heterophil antibody test became positive, 1 to 1,024. The total protein of the spinal fluid was elevated without cellular increase.

In 1934, Hiller and Fox reported a case of infectious neuronitis complicating infectious mononucleosis. This patient developed lymphadenopathy, splenomegaly, a heterophil antibody test positive to 1 to 125 and subsequently, a motor paralysis of the lower extremities of an ascending type. The spinal fluid contained markedly elevated protein with no increase in the cell count. The authors believed that the entire picture could be explained on the basis of infectious mononucleosis complicated by the Guillain-Barré syndrome.

The case presented here developed the clinical picture of infectious mononucleosis; the patient had typical blood smears and positive heterophil antibody tests. He developed signs of severe central nervous system involvement with markedly elevated spinal fluid protein and only a modest increase in cells.

CASE REPORT

A nineteen year old white, male soldier was admitted to the medical service on March 30, 1946, with complaints of weakness and a slight headache beginning two days before entry. The night before admission the patient became dizzy when walking to the latrine and almost fainted. Examination upon admission revealed a well developed young male with no positive physical findings other than a mild follicular tonsillitis and an enlarged cervical lymph gland at the angle of the mandible on the right side.

The second day after admission the patient got up to shave and was seen to stagger. Suddenly he fell to the floor, making wide purposeless movements of his limbs. When seen by a medical officer ten minutes later he was unresponsive, making aimless motions with his limbs. Blood ran from a corner of his mouth. Urinary and fecal incontinence were present. The pupils were widely dilated and failed to respond to light. Discs were normal, no nuchal rigidity was found. All reflexes were hyperactive and bilateral ankle clonus was noted. No Babinski reflex was elicited. Blood pressure was 112/?, temperature 101°F., respiration was not labored and the pulse was rapid but of good quality. He showed poor response to sedation and a lumbar puncture was performed under the most trying conditions. The spinal fluid was clear and did not appear to be under increased pressure but accurate pressure readings could not be obtained because the patient was thrashing around so violently. Immediately after the seizure, blood was drawn for analysis and revealed blood sugar 100 mg. per cent and blood calcium 11.3 mg. per cent. Examination of the spinal fluid (Table III), revealed no increase in the cell count but markedly elevated total protein, 340 mg. per cent, moderately elevated sugar, 93 mg. per cent and chlorides, 800 mg. per cent. Culture of the spinal fluid was subsequently reported negative. At this time the diagnoses considered were: epilepsy, intracranial hemorrhage, intracranial tumor, and in view of the albuminocytologic dissociation, Guillain-Barré syndrome although it was unlikely in view of the rapid onset with convulsions.

The following morning the patient's temperature went to 103.6°F., and he showed marked nuchal rigidity and positive Brudzinski's and Kernig signs. He was still comatose and restless; his reflexes remained unchanged. At this point the diagnosis was encephalitis, cause unknown and he was transferred to the contagious service. The white blood count was reported as 18,000, polymorphonuclears 40 per cent and lymphocytes 60 per cent. (Table I.) The differential smear showed many atypical lymphocytes, a large number having deeply basophilic cytoplasm, vacuolated with a foamy appearance. Many cells were fragmented. The nuclei were round, oval or indented, staining deeply and occasionally fenestrated. On the strength of the presence of these atypical forms, a heterophil antibody test was done and the following day reported positive through 1 to 1,792 dilution. (Table II.) Lumbar puncture this day revealed 96 cells (62 lymphocytes, 34 polymorphonuclears), total protein 320 mg. per cent, a negative culture and a negative spinal fluid Wassermann.

TABLE I
WHITE BLOOD COUNT

Date	April 2	April 6	April 15
Total count	18,000	11,500	11,150
Polymorphonuclears	40%	32%	57%
Lymphocytes	60%	68%	43%
Morphology	many atypical lymphocytes	many atypical lymphocytes	normal

TABLE II
HETEROPHIL ANTIBODY TESTS

Date	Dilution
April 3	1–1792
April 6	1–448
April 9	1–896
April 15	1–224
April 25	1–112
April 30	1–56
May 20	negative

On April 4th, the patient, still remaining comatose, restless and unresponsive, developed a right hemiplegia with paralysis of the right face of the peripheral type. Conjugate deviation of the eyes to the left was noted. Nystagmus was present with the quick component to the left. Reflexes on the right side became markedly hyperactive, a Babinski's sign appeared as well as a suggestive Hoffman's sign. Reflexes on the left side were sluggish. A grasp reflex was present in the left hand and strength remained

good on the whole left side of the body. A homonymous hemianopia was present on the right side and sensation was definitely diminished on the right, or paralyzed side of the body. Speech was incoherent and represented a motor aphasia.

constantly been to the right. Periods of apnea developed and became more marked and prolonged.

April 8th, marked the peak in the course of the disease. Upon examination the eyes were now seen to deviate to the right; the right

TABLE III

CEREBROSPINAL FLUID ANALYSES

Date	April 1	April 3	April 6	April 8	April 15	April 30
Appearance	clear	clear	clear	clear	clear	clear
Cells	normal	96 (162, P 34)	9 lymphs	248 (1230, P 18)	normal	normal
Protein	340 mg. %	320 mg. %	240 mg. %	216 mg. %	163 mg. %	39 mg. %
Sugar	93 mg. %	77 mg. %	60 mg. %	54 mg. %		
Chlorides	800 mg. %		600 mg. %	600 mg. %	660 mg. %	
Culture	negative	negative	negative			
Wassermann		negative				

By April 6th, the patient was more quiet and the purposeless movements were fewer, but the aphasia and hemiplegia remained unchanged. A Kahn test was reported negative. Lumbar puncture was repeated this day and normal pressure readings were obtained. Initial pressure 165 mm. of water. Spinal fluid findings were: clear fluid, 9 cells (all lymphocytes) and total protein 240 mg. per cent. The white blood count was 11,500, lymphocytes 68 per cent, polymorphonuclears 32 per cent and it again showed many atypical forms.

At midnight on April 7th, the patient suddenly went into a convulsion; there were clonic movements of all the limbs and twitchings of the facial musculature. Breathing became stertorous and rapid and he vomited large amounts of brownish fluid. Some of the vomitus was aspirated and suction via nasal catheter was carried out immediately. Respirations remained noisy and trismus was marked. Three hours later the patient convulsed again. Jacksonian movements of the jaw and facial muscles predominated. During this time he was incontinent and the pulse varied widely from 48 to 128 per minute. At 0500 hours the next morning respirations became Cheyne-Stokes in type. It was noted that at this time during the convulsions the ocular deviation was to the left, whereas for the preceding days of illness deviation had

homonymous hemianopia was still present. In addition to the right hemiplegia, the left side was now paralyzed and reflexes on the left had now become hyperactive. However, no Babinski reflex was elicited on the left. The aphasia remained pronounced. The periods of apnea in Cheyne-Stokes respiration were alarming, coma seemed more profound than at any previous time and recovery appeared doubtful.

Thereafter, the patient began to improve. The fever which had previously run 100° to 103°F. fell gradually to reach normal on April 11th. Pulse and respirations levelled off. By April 10th, response to painful stimuli was definite on the right side and the left arm moved impulsively. On April 11th, the eyes were moving freely in all directions with no dissociation and vision was apparently returning to the right eye. Speech remained affected and only a few words could be made out. On April 15th, the patient got out of bed unassisted. On the same day the heterophil antibody test had fallen to 1 to 225 and in the blood smear the normal ratio of polymorphonuclears to lymphocytes had returned. Two nights later and for several nights to follow, he apparently had hallucinations while asleep, crying out and seeing objects run across the ceiling. By April 22nd, these had disappeared and a slight speech impediment,

in addition to memory defects, were all that remained.

Examination on May 14th, revealed no positive physical findings and the neurologic examination was negative. All laboratory tests had returned to normal. The boy had some difficulty recalling parts of his army career and he tired readily; otherwise, he felt well. On May 26th, the patient was discharged from the hospital on convalescent furlough.

In this patient the onset of the central nervous system involvement followed within two days the development of tonsillitis and lymphadenopathy. Two days following this the heterophil antibody test was strongly positive, blood smears were typical and the spinal fluid protein was markedly elevated. The almost simultaneous onset of these symptoms and signs would seem to indicate that only one disease was present and that the disease was capable of protean manifestations. In view of the history, the clinical findings and the blood picture it is logical to explain all the manifestations as due to infectious mononucleosis.

SUMMARY

A case is presented of infectious mononucleosis with severe central nervous system involvement as evidenced by transitory paralyses, right homonymous hemianopia and marked rise in spinal fluid protein. Subsequently, all clinical signs and laboratory data returned to normal.

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Book Review

An Integrated Practice of Medicine. By Harold Thomas Hyman, M.D. Volumes I, II, III and IV and Index. Pp. 4,131, with 1,184 illustrations, 305 in color. Philadelphia, 1947. W. B. Saunders Company. *Price* $50.00 per set.

"An Integrated Practice of Medicine" is an effort to present in four volumes a complete textbook for the general practitioner. Omitting only elective major surgery, in the words of the author it "supplements the material of internal medicine with authoritative text devoted to the clinical subjects of Infection, Tropical Medicine, Allergy, Metabolic Disorders, Poisonings, Toxicology, Neoplastic Disease, Cardiology, Hematology, Endocrinology, Psychiatry, Neurology, Ophthalmology, Dentistry, Dental Surgery, Gastro-Enterology, Proctology, Otology, Rhinolaryngology, Urology, Gynecology, Obstetrics, Pediatrics, Orthopedics, Dermatology, Minor Surgery, Anesthesiology, Emergency Surgery, Convalescence and Rehabilitation. It includes brief but complete and accurate surveys of the preclinical sciences of Anatomy, Serology, Immunology and Physiological Chemistry, as well as meticulous details of the practical clinical disciplines of Physical Diagnosis, Laboratory Methods, Clinical Pathology, Pathologic Physiology, Electrocardiography, Dietetics, Radiology, Prognosis, Pharmacology and Therapeutics."

Obviously, to attempt to place so much material within the confines of approximately four thousand pages is an ambitious undertaking. It is noteworthy that the author and his various specialist associate editors have been able to accomplish their purpose so well. From the viewpoint of the general practitioner requiring brief discussions often seasoned with the author's advice, or wishing to refresh his memory quickly on a wide variety of topics, this book should be of great value. On the other hand, it should be emphasized that this is no reference work and is in no way comparable to one of the authoritative systems of medicine.

The work is divided into twenty-five sections, each of which covers some general field, such as infection, allergy, pediatrics or the respiratory system, and many of which have been written with the aid of a more specialized associate editor. Each section is then broken down into chapters discussing in turn specific topics. When possible the presentation follows the pattern: etiology, epidemiology, pathology, clinical manifestations, course, diagnosis, complications, prognosis, active treatment, preventive treatment and occasional special leads, e.g., in rheumatic fever, marriage and pregnancy, and surgery in cases of rheumatism.

The composition is exceptionally readable, ordinarily factual even if sometimes commonplace, and given to practical detail; it is scattered with the author's opinions, and considerably helped by frequent cross references. Some 319 tables of differential diagnosis are included. It may be noted that brevity of presentation frequently interferes with completeness but on the whole an amazing amount of practical though general information is given. Each volume contains its individual index and in addition a separate full index volume aids in the quick location of topics. The test is studded with really first class illustrations. The volumes are well bound and printed and are not so large or heavy as to be unwieldy. A selected bibliography for physicians resident in small towns or cities without library facilities is given.

For the general practitioner, for whom this work is primarily intended, the author and his colleagues have done an excellent job.

F. K. H.